Alpha2-adrenergic receptor agonists in myocardial ischemia

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(Met dank aan Simon Braat)

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In memory of my father
To my mother
To Monika, Anouk, Esmée and Nona, with love

Contents

CHAPTER 1

Introduction

Despite continuing improvements in anesthetic and surgical techniques, it is expected that perioperative cardiac morbidity and mortality will continue to increase because of the rapid aging of the surgical population and greater prevalence of more advanced coronary artery disease.[1] Solution of this problem requires identification of the predictors of adverse perioperative cardiac outcome, followed by therapeutic trials aimed at modifying these predictors in an effort to decrease morbidity and mortality. Perioperative outcome studies have identified preoperative, intraoperative and postoperative predictors of perioperative cardiac morbidity.[1] The most important preoperative predictors of cardiac outcome are unstable coronary syndromes, decompensated congestive heart failure, significant arrhythmias and severe valvular disease. The classic intraoperative predictors include emergency surgery, vascular surgery, prolonged thoracic or upper abdominal surgery and hypotension and tachycardia. It was recently shown by Mangano and co-workers that the single most important predictor of adverse cardiac outcome was early postoperative myocardial ischemia.[2,3] Such postoperative ischemia conferred a ninefold increase in the odds of experiencing cardiac death, a nonfatal myocardial infarction, or unstable angina.

These results suggest that prevention and therapy for perioperative - and especially postoperative -ischemia may hold the key to reducing perioperative cardiac morbidity. There are very few randomized trials of medical therapy before surgery to prevent perioperative myocardial ischemia, and they do not provide enough data from which to draw firm conclusions.[4-12] Studies in non-surgical patients have suggested that the alpha$_2$-adrenergic receptor agonist clonidine has anti-anginal and ischemia-limiting effects.[13-14] Recently, several studies have evaluated the use of alpha$_2$-adrenoreceptor agonists during the perioperative period.[15] Most of these studies have concentrated on their sedative, sympatholytic and hemodynamic stabilizing effects. The present series of investigations was initiated in order to study possible mechanisms for the potential anti-ischemic effect of the new alpha$_2$ agonists dexmedetomidine and mivazerol, and to gain information on the possible usefulness of these drugs as anesthesia adjuvants in high-risk cardiovascular patients at risk for coronary artery disease.

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CHAPTER 2

Review of the literature on perioperative myocardial ischemia

2.1. Myocardial ischemia

In the heart, a complex relation exists between contraction and perfusion. While cardiac contraction generates the driving pressure required for perfusion of all organs including the heart, systolic contraction impedes myocardial perfusion. The exact mechanism of this impediment is not entirely understood, but it is undoubtly more pronounced in the endocardial than in the epicardial layers. As a consequence, the endocardial layers are perfused almost exclusively during diastole. Nevertheless, perfusion of the myocardium is matching demands under all physiological conditions, including the most severe physical exercise, and blood flow in the endocardial layers is equal to or slightly higher than the epicardial blood flow (endo-/epicardial blood flow ratios 1.0-1.1). To match supply with demand, the heart possesses a powerful autoregulation, which means that very small parts of the myocardial muscle regulate their own perfusion, presumably by feedback through arteriolar content of oxygen and metabolites like CO_2, H^+, and adenosine.[1] So, as long as the heart functions within its autoregulatory range, cardiac work determines perfusion. The opposite is true when myocardial perfusion is impaired, for example by obstruction of a coronary artery. In that case, myocardial function rapidly deteriorates. Under these conditions, the endocardial layers are most at risk for underperfusion. During moderate stenosis, endocardial blood flow can decrease below 50% of normal while epicardial blood flow may still be normal or even higher.[2,3] This is due partly to the limited time for perfusion of the endocardial layers, but is believed to be also partly due to "steal" of endocardial blood flow by the epicardial layers: if perfusion in a vascular bed is entirely pressure dependent, dilation in one part of the bed may decrease blood flow to another part of the same bed.[1,4] For these reasons, coronary stenosidues gradually leads to endocardial ischemia. When obstruction of the coronary vessel is complete, epicardial blood flow is severely compromized also and transmural ischemia occurs. Myocardial ischemia occurs because of a mismatch of oxygen supply and demand. Coronary obstruction due to atherosclerosis, emboli or thrombosis obviously leads to reduced supply. In the presence of any obstruction, hypotension and tachycardia may reduce supply further. Tachycardia reduces supply because it decreases the diastolic time interval, available for coronary perfusion. Because tachycardia also increases myocardial oxygen demand considerably, it is ussually the highest risk factor for induction of ischemia, and is clinically used to provoke ischemia by pacing the patient's heart at higher heart rate.

Hypotension may decrease coronary perfusion because, in the presence of reduced perfusion pressure, the ischemic region and especially the endocardial layers are already maximally vasodilated, and any further drop in pressure will affect perfusion. For that reason, vasodilators may, through systemic or coronary vasodilation, worsen myocardial ischemia, especially in the endocardium. This phenomenon is known as "coronary steal".[5-7] Nathan and Feigl studied the effect of alpha-adrenergic vasoconstriction on the transmural distribution of myocardial blood flow.[8] They showed that, during normal perfusion as well as during ischemia, alpha-adrenergic stimulation decreased epicardial blood flow and increased endocardial blood flow, thus producing a "reverse-steal" effect. To what extent this reverse-steal effect may improve myocardial ischemia in the clinical situation is, until now, incompletely understood.

2.2. Perioperative autonomous reactions affecting myocardial ischemia

The major body injury induced by surgery/anesthesia and by the recovery from surgery/anesthesia evokes a stress response. [9-12] Perioperative factors like pain, anxiety, the presence of an endotracheal tube, and physiological derangements like hypoxia, hypercarbia, hypothermia, intravascular volume overload or depletion may all evoke these responses. They consist of stimulation of the hypothalamus-pituitary-adrenal axis, renin-angiotensin axis, and the sympathetic nervous system.
Levels of hormones like vasopressin, insulin, growth hormone, and aldosterone become elevated. Moreover, high levels of anti-insulin hormones like epinephrine, cortisol, and glucagon induce endogenous hepatic glucose production and reduced glucose uptake which results in hyperglycemia. Therefore, the major fuel of the body becomes fat, while proteins are catabolized also. Especially fatty acids are considered to be harmful for the ischemic heart, because they increase the oxygen cost of ATP production and may make the heart more suceptible to arrhythmias.[13] An important aspect of the effect of surgical stress on myocardial ischemia are the changes in cardiovascular function. Infusions with cortisol, glucagon and epinephrine demonstrated a synergistic effect of the three hormones on the rate-pressure product.[11] However, with respect to the ischemic heart, sympathetic stimulation is the most important factor in the stress response.

2.3. Sympathetic stimulation

Norepinephrine is the transmitter at most postganglionic sympathetic nerve endings and at several synapses in the central nervous system, especially in the hypothalamus. In the adrenal medulla, not only norepinephrine, but especially epinephrine is secreted. After their secretion, both adrenergic agents are transported through the blood to their target organ. Catecholamines stimulate alpha and beta receptors. Alpha-receptor stimulation causes vasoconstriction, beta-1 receptor stimulation causes increased cardiac chronotropy and inotropy and beta-2 receptor stimulation

causes vasodilation. The serum levels of the catecholamines norepinephrine, epinephrine and dopamine have been observed to increase after a variety of stresses. Surgical stress increases the levels of these hormones, but the highest levels have been observed immediately after the end of surgery and anesthesia.[14] Plasma epinephrine concentrations reflect adrenomedullary secretion, whereas plasma norepinephrine concentrations are used as an index of sympathetic nervous system activity. It is important to realize that most of the norepinephrine released at post-ganglionic neuro-effector sites is removed from the synapse by re-uptake into the nerve ending. The excess spills over into the circulation and can be measured.
Tachycardia and hypertension appear to be associated with increased levels of circulating norepinephrine[10,11] and may result in increased myocardial oxygen demand and reduced supply at higher heart rates. These changes in catecholamines are associated with parallel increases in platelet aggregation and reduced fibrinolytic activity.[15-17]

2.4. Anesthesia and perioperative myocardial ischemia

There are three categories of potential etiologies for perioperative myocardial ischemia. A first category includes the factors associated with the myocardial oxygen demand-supply ratio. Decreased supply can be due to hypoperfusion, redistribution or spasm and increased demand is usually related to stress response phenomena. A second categorie includes factors associated with thrombosis, e.g. inflammatory response, leucocyte activation, plaque rupture/spasm, hypercoagulable state. And a third categorie includes coronary artery factors (shear stress/spasm, endothelial factors, embolism).[18]
Postoperatively, the incidence of ischemia is significantly higher than intraoperatively or preoperatively. It is also well documented that the termination of anesthesia and surgery, with emergence and transition into the postoperative period, is associated with continued activation of the sympathetic nervous system. Plasma catecholamine levels are usually higher in the immediate postoperative period than during surgery. Increased levels of circulating norepinephrine appear to be associated with tachycardia and hypertension and may result in increased myocardial oxygen demand and reduced supply at higher heart rates.[10,11] In the presence of a compromized circulation, the imbalance between supply and demand could lead to myocardial ischemia and, possibly, serious adverse outcome.[19-21] Elevated plasma catecholamines are also associated with accelerated coagulation and this hypercoagulable state may also increase the incidence of ischemia. These findings suggest that increased sympathetic nervous system activity is a key factor for the increased incidence of myocardial ischemia.
These factors contribute to the perceived need for greater control of the hyperadrenergic state and the postoperative stress response, which has implications for metabolism, the immune response, coagulation, and the cardiovascular system, and which may have an important impact on outcome.

2.5. Reducing perioperative myocardial ischemia

There are a variety of options for reducing peri-operative cardiac morbidity:

2.5.1. Increasing anesthetic depth

Intra-operatively, the incidence of myocardial ischemia is not significantly different from the incidence of pre-operative ischemia, despite the many stresses affecting intra-operative myocardial demand for oxygen, as long as hemodynamics are well controlled.[22] It appears that anesthetics or the anesthetic-like state may have protective effects against surgical stress. This protective effect of anesthesia during surgery however is not fully maintained during the emergence. Recent findings suggest that inhalation anesthetics, moderate levels of narcotics, or regional anesthesia by intrathecal or epidural anesthetics substantially decrease the intra-operative stress response, including the increased level of circulating catecholamines.[23-25] Whether anesthetics prevent the increase of ischemia by controlling hemodynamic variability, preventing surges in catecholamines, antinociception, or through an unknown anti-ischemic effect, has not been determined. However, it is clear that the anesthetic state is able to protect the myocardium from stressful events which would otherwise lead to ischemia.
Opioids are known to decrease heart rate, wall tension, pain and circulating levels of plasma catecholamines without depression of ventricular function. It is therefore not surprising that extending anesthesia with opioids for 18-24 hours postoperatively blunts the stress response and reduces perioperative morbidity.[26,27]

2.5.2. Regional anesthetic techniques

It is well documented that the combination of general anesthesia with epidural anesthesia and analgesia intraoperatively and postoperatively, can smooth the transition from surgery to postoperative recovery and in this way can reduce postoperative morbidity. The typical postoperative increase in heart rate is reduced threefold when epidural anesthesia and analgesia is used after aortic surgery.[28] Reiz and co-workers showed that patients undergoing emergency vascular surgery in the face of recent myocardial infarctions had a lower incidence of ischemia and ventricular dysfunction and a lower reinfarction rate when they were randomized to receive epidural anesthesia and analgesia.[29]
Yeager and colleagues demonstrated that high-risk patients had far fewer cardiovascular, infectious, and overall complications when they received epidural anesthesia and analgesia compared with a general anesthetic technique.[30] Tuman and co-workers studied the effect of epidural anesthesia and analgesia on coagulation and outcome after major vascular surgery.[31] They found less thrombotic complications in the patient group receiving general anesthesia plus epidural anesthesia and analgesia versus the patient group receiving general anesthesia alone. The perioperative ischemia randomized anesthesia trial (PIRAT) study randomized 100 patients under-

going lower extremity revascularization to receive epidural anesthesia and analgesia or general anesthesia.[32] Regional anesthesia was associated with lower catecholamine levels and fewer vascular graft occlusions.
Blomberg and co-workers used Thoracic Epidural Anesthesia (TEA) in the treatment of myocardial ischemia in patients with severe angina pectoris unresponsive to multiple medical regimens and found that TEA achieved more than mere control of pain.[33] TEA reduced myocardial oxygen demand by decreasing systolic arterial blood pressure, heart rate, and pulmonary capillary wedge pressure without significant changes in coronary perfusion pressure or cardiac output. Several possible mechanisms exist for these salutary effects of TEA. On a global basis, TEA decreases myocardial oxygen demand.[34,35-38] Reduction in wall stress, heart rate, and inotropy have all been reported. Despite the potential for a coronary steal, improvements in perfusion to ischemic areas have been observed.[35, 39-42] This effect may be on the basis of reduced left ventricular wall pressure with a redistribution of blood flow to the subendocardial layer. Conversely, TEA decreases cardiac autonomic tone and thus may favorably alter the endo/epicardial blood flow ratio. However, this mechanism is thought to be only a minor determinant of transmural coronary blood flow.[43-45] TEA also alters myocardial metabolism and reduces the uptake of catecholamines.[36,37,43] Sympathetic blockade may inhibit lipolysis within the ischemic area, thereby decreasing regional myocardial oxygen consumption and reducing the severity of the ischemic injury. Finally, the possible effect of sympathetic blockade on coronary vasoconstriction distal to coronary stenoses is apt to be involved. Heusch and colleagues have shown that sympathetic poststenotic vasoconstriction can be blocked by epidural anesthesia.[40-42] Poststenotic ischemia may activate further sympathetic discharge via spinal reflexes, and produce a positive feedback mechanism leading to a vicious cycle of progressive vasoconstriction and worsening of myocardial ischemia. The persistent therapeutic effect of TEA in alleviating ischemia may be due to blocking of this feedback mechanism.

2.5.3. Control of hemodynamic instability

Control of blood pressure, heart rate, cardiac output, and vascular resistance with a variety of interventions that attenuate the cardiovascular effects of perioperative sympathetic hyperactivity has been shown to impact positively on cardiovascular outcome.[22]
Berlauk and co-workers showed that intensive perioperative care facilitated by the use of prolonged invasive hemodynamic monitoring is associated with a markedly reduced rate of graft occlusion after peripheral vascular surgery.[46]

2.5.4. Beta-blockers and calcium-antagonists

Three limited studies have examined the use of perioperative beta-blockers. Stone et al gave oral beta-blockers 2 hours before surgery to a randomized group of patients with mild hypertension who had predominantly (58%) vascular surgery.[47] Control

subjects had a higher frequency (28%) of ST-segment depression than treated patients (2%). In a nonrandomized study, Pasternack gave oral metoprolol immediately before surgery and followed with intravenous drug during abdominal aortic aneurysm repair.[48] Only 3% suffered an acute MI, compared with 18% for matched controls. In a later report, the same author reported less intraoperative ischemia in patients treated with oral metoprolol before peripheral vascular surgery.[49] Calcium entry blockers alone do not appear to be effective in reducing the incidence of new perioperative myocardial ischemia. [50,51] This makes it unlikely that they have any direct impact on perioperative outcome.
No data yet exist to describe the impact on outcome of any strategy directed at detecting and systematically treating silent perioperative ischemia.

2.5.5. Nitroglycerin

Nitroglycerin has been shown to reverse myocardial ischemia intraoperatively. Prophylactic use of nitroglycerin in patients at high risk may have no effects, however, or may actually lead to cardiovascular decompensation through decreases in preload. Additionally, nitroglycerin paste or patch may have uneven absorption intraoperatively. Accordingly, nitroglycerin should usually be administered in the intravenous formulation, if required. Four controlled studies have evaluated the value of prophylactic nitroglycerin infusions for high-risk patients, including two studies in noncardiac surgery patients.[52-55] Only one study, performed in patients with stable angina undergoing carotid endarterectomy, demonstrated a reduced incidence of intraoperative myocardial ischemia in the group receiving 1 $\mu g.kg^{-1}.min^{-1}$ of nitroglycerin.[52] Neither of the two small studies demonstrated any reduction in the incidence of MI or cardiac death.

2.5.6. Improvement of the economy of myocardial oxygen usage

Inhibition of free fatty acid uptake in favour of carbohydrate metabolism should be advantageous during myocardial ischemia.[56]
Glucose-insulin-potassium solutions[57] and compounds which induce a pharmacological shift of cardiac metabolism with reduction in FFA utilization may be of clinical value.[58]

2.5.7. Improvement of blood flow through poststenotic vascular bed

Improvement in poststenotic blood supply by the administration of vasodilators is of limited value, since a greater degree of coronary steal might occur. Thromboxane A2 may be critically involved in the pathophysiology of myocardial ischemia by constricting blood vessels, inducing platelet aggregation and by increasing the permeability of cellular membranes. An attractive approach is to inhibit thromboxane synthesis selectively, thereby to redirect endoperoxide metabolism towards vasodilating prostacycline metabolites.[59]

Adenosine, adenosine regulating agents and nucleoside transport inhibitors are currently being investigated for their coronary vasodilatory and cardioprotective properties.[60]

2.5.8. Anticoagulation

It is possible that anticoagulation alone might benefit cardiovascular outcome in the high-risk surgical patient. In addition to reducing mortality rates after acute myocardial infarction, anticoagulation also lessens the rate of reinfarction. This finding in medical patients potentially has tremendous significance for surgical patients with a history of recent MI, because the mortality of perioperative reinfarction remains near 30% to 50%. Obviously, this needs to be examined rigorously before recommending even low-dose postoperative anticoagulation in high-risk patients. There is, however, at least one controlled randomized trial examining the effect of postoperative anticoagulation on outcome in high-risk cardiac patients undergoing lower extremity revascularization that has shown a lower incidence of vascular graft failure in anticoagulated patients as well as improved postoperative survival compared with controls.[61]

2.5.9. Reducing central sympathetic outflow

The above mentioned studies suggest that controlling the peri-operative stress response may attenuate peri-operative myocardial ischemia. Unfortunately, none of the interventions to blunt the stress-response is without complications. High levels of inhalation anesthetics will delay awakening. Narcotics also may delay awakening and cause post-operative respiratory depression, nausea and vomiting. Vasodilators which act directly on the vascular smooth muscle may induce reflex tachycardia and increased levels of circulating catecholamines.[62,63] Although vasodilators modulate preload and afterload, the resulting tachycardia may decrease the ratio of oxygen supply to demand significantly. Blocking some of the adrenergic receptors to achieve hemodynamic control will leave the action of the unblocked receptors unopposed. Epidural or intrathecal nerve conduction block reduces the intraoperative stress response but is not appropriate postoperatively for all patients. The use of anesthetics or high-dose analgesics is not clinically feasible for most patients postoperatively, when the incidence of ischemia and adverse outcome is highest.

The development of an anesthetic-like drug that could blunt the adrenergic response to the stresses of major surgery, thereby promoting hemodynamic stability, without causing respiratory depression would be ideal: alpha$_2$ -adrenergic receptor agonists appear to be promising candidates.

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CHAPTER 3

Review of the literature on alpha$_2$-adrenergic receptor agonists

This review will focus mainly on the potential benefits and risks of the perioperative use of alpha$_2$-adrenergic agonists, especially in patients with serious cardiovascular disease.

3.1. Alpha$_2$-adrenergic receptors

The original classification of adrenergic receptors into alpha and beta, based on their graded responses to a series of agonists, was made by Ahlquist in 1948.[1] The subclassification of alpha-adrenergic receptors was initially based on the presumed synaptic anatomical localization: presynaptic alpha$_2$ receptors and postsynaptic alpha$_1$ receptors.[2,3] This anatomic classification of alpha-adrenoreceptors was not supported for long because alpha$_2$-adrenoreceptors were also found postsynaptically, or even extrasynaptically.[4] Currently, the classification of alpha-receptors is based on their pharmacological characteristics, for instance, at the alpha$_1$-receptor, the antagonist prazosin is more potent than yohimbine, whereas at the alpha$_2$-receptors the reverse is true.[5] Different alpha$_2$-isoreceptors have recently been described in mammalian tissues. A pharmacological subdivision of alpha$_2$-adrenoreceptors into at least three alpha$_2$-isoreceptors (alpha$_{2A}$, alpha$_{2B}$, alpha$_{2C}$) has been suggested based on the affinities of different alpha$_2$-adrenoreceptor agonists and antagonists.[6] The existence of another class of receptors or binding sites resembling the alpha$_2$-adrenoreceptors has been indicated by both functional and radioligand binding studies. These sites bind selectively alpha$_2$-ligands that are either imidazolines (e.g. clonidine or idazoxan) or oxazolines (e.g. rilmenidine), but have very low affinity for agonists or antagonists without the imidazoline or oxazoline stucture, such as adrenaline and yohimbine.[7,8] Molecular biology has recently made it possible to obtain structural information on the alpha$_2$-adrenoreceptors.[9,10]
Beginning with the platelet-type alpha$_2$-adrenoreceptor,[11] three distinct human alpha$_2$-adrenoreceptor subtype genes or cDNAs have been cloned to date, designated alpha$_2$-C10,[11] alpha$_2$-C4[12] and alpha$_2$-C2,[13] according to the location of these genes on human chromosomes 10, 4 and 2. The alpha$_2$-adrenoreceptor is a member of the G-protein (guanine nucleotide binding proteins) coupled family of membrane receptors.[14] G proteins are needed to transfer the initial external stimulus from alpha$_2$-adrenoreceptors into a cellular response. Activated G proteins can either modulate the synthesis or availability of intracellular second messenger, or can directly alter the activity of transmembrane ion channels.[15]

3.2. Location and physiological functions of alpha$_2$-adrenoreceptors

Alpha$_2$-adrenorecptors exist in several tissues and organs of the body, and the functions mediated by these vary depending on the type of the adrenoreceptor and the tissue. Inhibition of neurotransmitter release from peripheral nerve endings is one of the most prominent actions ascribed to alpha$_2$-adrenoreceptors; [2] certainly the CNS actions are at least equally important. Most, if not all, of the central alpha$_2$ -receptors are postsynaptic. In the human brain, the highest density of alpha$_2$-agonist binding sites have been observed in the medullary dorsal motor complex, which may be the site of bradycardic and hypotensive effects of alpha$_2$-adrenoreceptor activation.[16] The locus coeruleus, which itself contains alpha$_2$-receptors, is the predominant noradrenergic nucleus in the brain and is an important modulator of vigilance.[17] High densities of alpha$_2$-agonist binding sites have also been demonstrated in the intermediolateral cell column, the substantia gelatinosa and the motor nuclei of the ventral horn of the human spinal cord.[16,18] Peripheral tissues contain both presynaptic alpha$_2$-adrenoreceptors on sympathetic nerve endings and postsynaptic alpha$_2$-adrenoreceptors on target cells, where they have distinct physiological functions.[19] For example, in arterial and venous smooth muscle, they mediate vasoconstriction.[20-22]

3.3. Pharmacology of alpha$_2$ agonists

Clonidine is the prototypical alpha$_2$-adrenoreceptor agonist to which all other alpha$_2$ agonists are compared.[23-25] Its actions are mediated mainly by central pre-and postsynaptic alpha$_2$-adrenoreceptors but it is a weak alpha$_1$-agonist as well.
In humans, clonidine has been used for the treatment of mild or moderate hypertension for more than a decade.[26] It has also been investigated extensively as an adjunct to anesthesia.[27,28] Clonidine is an imidazoline derivative with a distribution half life (iv) of approximately 10 min and an elimination half life (iv) of approximately 8.5 hours.[24]
Mivazerol[29] and dexmedetomidine[30-32] are novel alpha$_2$ agonists with high affinity to alpha$_2$-adrenoreceptors. These new drugs have a considerably higher alpha$_2$/alpha$_1$-selectivity ratio than clonidine and are more potent as alpha$_2$ agonists. Dexmedetomidine has a distribution half life (iv) of approximately 5 min and an elimination half life (iv) of approximately 2.3 hours.[33]

3.4. Physiologic responses mediated by alpha$_2$-adrenoreceptors

The predominant effect of alpha$_2$ agonists, such as clonidine, is on receptors within the CNS which bring about a baroreceptor-mediated decrease in sympathetic tone and a concomitant increase in parasympathetic vagal outflow.[23,25] This results in reduction in blood pressure and heart rate, as well as a decline in plasma catechola-

mine concentrations. These agents act within the medullary system to increase the gain and decrease the set-point of the baroreceptor reflex, thus maintaining blood pressure at a lower level. At the same time, stimulation of peripheral postjunctional alpha$_2$-receptors on vascular smooth muscle causes vasoconstriction, tending to raise blood pressure.[20-22] Higher blood levels of the drugs are required for this peripheral action than for the central effects.This mode of action is in marked contrast to the blood-pressure lowering actions of peripherally acting direct vasodilators, such as nitroprusside.[34,35] It is also different from the effects of other types of drugs acting on peripheral structures of the autonomic nervous system: ganglionic blocking agents (trimethaphan), drugs depressing the postganglionic adrenergic neurons (reserpine, guanethidine), cardiac beta-blocking drugs, which may lower blood pressure by decreasing heart rate, contractility, and cardiac output, or by drugs that prevent vasoconstriction by blocking alpha$_1$-adrenergic receptors on vascular smooth muscle (prazosin). In all these cases, the central homeostatic cardiovascular control system can be expected to oppose the actions of these drugs that directly inhibit effector systems.[34-37] The resultant increased activity of the nonblocked portions of the system (eg, reflex tachycardia) may result in increased rather than decreased metabolic activity and myocardial oxygen demand. In contrast, the alpha$_2$ agonists regulate autonomic activity by acting on the control mechanisms themselves, and thus achieve a more physiologic, coordinated or balanced blood pressure control.
In addition to these antiadrenergic and hemodynamic effects, these drugs are sedatives, anxiolytics and powerful analgesics, with antisialagogue and antiemetic properties. Clonidine's actions in decreasing anesthetic requirements seem related to its attenuating effect on central noradrenergic transmission. For a complete discussion of the possible mechanisms by which anesthesia is produced by stimulation of central alpha$_2$-receptors, see the review by Maze and Tranquilly.[38] The mechanisms of the analgesic actions of alpha$_2$ agonists have not been fully elucidated.[39]

This combination of actions makes it clear why these drugs are of interest in anesthesia today. If appropriately used, these compounds may produce an ideal pharmacodynamic profile for an adjunctive agent for clinical anesthesia.[38] While clinical experience with the modern, specific alpha$_2$ agonists is limited, clonidine has been used extensively.

3.5. Benefits of clonidine during the perioperative period

3.5.1. Decreased doses of anesthetic and analgesic drugs

There are many sedative and hypnotic drugs that potentiate general anesthetics, including the barbiturates, benzodiazepines, and opioids. Opioids are effective analgesics and also smooth out hemodynamics and decrease the stress response to some extent. However, almost all of the other anesthetic-sparing and analgesic drugs produce these effects at the cost of prolonged awakening. In the case of the opioids, postoperative respiratory depression may necessitate artificial ventilation. Clonidine

and the other alpha$_2$ agonists have not been reported to be respiratory depressants, except occasionally in cases of massive, accidental overdose. The lack of respiratory depression from alpha$_2$ agonists, as well as their lack of potentiation of narcotic-induced respiratory depression, is supported by the fact that patients treated with clonidine in a CABG study were extubated significantly sooner as compared to patients in the control group.[40]

3.5.2. Improved hemodynamic stability

In several clinical studies in patients undergoing cardiac or major vascular surgery, it was shown that clonidine could decrease episodes of high blood pressure and tachycardia.[40-42]

We've been using in our department clonidine for more than 10 years for hemodynamic stabilization in the immediate postoperative period after cardiac surgery. The next table shows the hemodynamic effects of 150 µg of clonidine, given slowly iv over 10 min in 24 cardiac surgical patients with postoperative hypertension (unpublished data, Van Vliet J and Roekaerts P, 1995).

Clonidine 150 µg iv	before infusion	10 min after end of infusion
mean arterial pressure (mmHg)	101 ± 12	78 ± 15*
heart rate (beats·min^{-1})	107 ± 16	99 ± 14
cardiac index (L·Kg^{-1}·min^{-1})	3.9 ± 1.1	3.3 ± 0.6*
LV stroke work index (gm·m^{-2})	48 ± 11	37 ± 10*
Pulmonary capillary wedge pressure (mmHg)	9 ± 5	7 ± 3
Systemic vascular resistance (Ds·cm^{-5})	1106 ± 356	891 ± 276*

These data indicate that, in these patients, clonidine can significantly decrease blood pressure, cardiac index, LV stroke work index and systemic vascular resistance, with a moderate decrease in heart rate.

The primary aim of careful control of blood pressure and heart rate during and after anesthesia and surgery in patients with cardiovascular disease is prevention of myocardial ischemia. The effect of premedication with clonidine on the incidence of ischemic ST-segment changes in the pre-bypass period was reported by Kent et al[43] and by Dorman et al[44] Both groups reported less ischemia in clonidine-treated patients than in a control group. In a non-surgical population, it had been shown previously that clonidine could improve the myocardial oxygen supply/demand ratio in ischemic heart disease and reduce attacks of angina pectoris.[45,46]

Clonidine appears to affect both myocardial oxygen supply and demand beneficially by reducing sympathetic outflow to the systemic vascular bed and to the heart. Moreover, in the heart it reduces beta-adrenergic and alpha-adrenergic (both alpha$_1$ and alpha$_2$) effector systems. By acting on central control systems, clonidine does this in a well-coordinated fashion. Whereas beta-adrenergic blocking drugs deal only

with heart rate and contractility, the alpha$_2$ agonists also reduce adrenergically mediated vasoconstriction, including coronary vasoconstriction, which may have in fact been exacerbated by the use of a beta-blocker alone.

3.5.3. Sympatholysis

In patients undergoing coronary artery bypass grafting surgery, it has been demonstrated that pre- and intraoperative clonidine therapy maintained significantly lower plasma catecholamine levels during episodes of major noxious stimuli when compared to control patients.[40,47,48]
In the clonidine-treated patients in one CABG study the lower levels of norepinephrine and epinephrine (compared with the control group) continued into the immediate postoperative period, [40] which is the time when these patients are the most likely to suffer from hyperdynamic and ischemic episodes. In aortic surgery, Quintin et al found similar results, with plasma levels of both catecholamines significantly lower in clonidine-treated patients before, during, and after cross-clamping.[42,49] This decreased adrenergic response in aortic surgery has been confirmed by others.[41]

3.5.4. Decreased postoperative shivering

Shivering is common in patients after major surgery. In order to supply the increased oxygen required by the shivering tissues, the respiratory and circulatory systems are severely taxed. Oxygen consumption and carbon dioxide production have been found to increase by up to 500% above basal levels.[50-52] If cardiac output cannot increase sufficiently, or if hypoxemia and/or anemia are also present, oxygen transport may not keep pace with metabolic demand. Thus, disproportional tissue oxygen extraction may occur, causing mixed venous and sometimes arterial desaturation and lactic acidosis.[50-54] It is well known that central adrenergic systems influence temperature regulation,[55-56] and there are laboratory reports of suppression of shivering by clonidine.[57] In the study by Flacke and colleagues of patients undergoing CABG surgery, it was observed that the incidence of shivering in the immediate postoperative period was significantly reduced by clonidine. Since then, several more formal investigations have pointed out the efficacy of clonidine in suppressing postanesthetic shivering, as well as in decreasing total body oxygen consumption in the immediate postoperative period.[58-62] This decreased postoperative oxygen consumption together with the increased cardiovascular and sympathoadrenal stability may be of clinical importance in certain high-risk patients with compromised oxygen supply-and-demand balance.

3.6. Potential side effects

Potential side-effects of alpha$_2$-adrenoreceptor agonists in the high-risk patient population are bradycardia, hypertension and hypotension.[63] Bradycardia is usually beneficial in these patients, but, should it require treatment, responds easily to the

administration of atropine iv. Hypertension occurs mainly when the alpha$_2$-adrenoreceptor agonists are administered as a large, rapid intravenous bolus. This effect can be avoided by using a slower infusion. The hypotension associated with the alpha$_2$-adrenoreceptor agonists usually is limited to a 20% decrease in blood pressure in healthy patients, but can decrease further in chronically hypertensive patients with high basal sympathetic tone. Alpha$_2$-adrenoreceptor agonist-induced hypertension is mainly peripherally-mediated, hypotension is centrally-mediated. Because these cardiovascular effects of alpha$_2$ agonists might be overcome pharmacologically by peripheral-acting vasoactive drugs,[64] the benefits of low sympathetic activity and circulating catecholamines associated with the use of alpha$_2$ agonists are retained (see also chapters 4 and 5). Sedation is considered a side-effect in ambulatory patients. The sedative effect is desirable in patients who will remain hospitalized post-operatively, but not in patients who will be discharged from the hospital on the day of surgery. However, specific alpha$_2$-adrenoreceptor antagonists are available[65] which also antagonize the central effects of the alpha$_2$ agonists (see chapters 5 and 6).

3.7. Limitations of clonidine therapy in patients with ischemic heart disease

Previous reports, although limited, have suggested that the non-specific alpha$_2$ agonist clonidine, because it can produce perioperative hemodynamic and adrenergic stability and also because it can reduce attacks of angina pectoris in patients with coronary artery disease, could be especially beneficial as a perianesthetic adjuvant in patients with ischemic heart disease.

On the other hand, alpha$_2$-adrenoreceptor stimulation also causes coronary vasoconstriction. Studies on the effects of alpha$_2$-adrenoreceptor activation during experimental myocardial ischemia have yielded conflicting results. Heusch reported that alpha$_2$ excitation by sympathetic nerve stimulation and exercise could induce myocardial ischemia.[66] This regional myocardial ischemia further activated cardiac sympathetic nerves, thus inducing alpha$_2$-adrenoreceptor vasoconstriction of the poststenotic vascular bed and further aggravation of myocardial ischemia. However, systemic administration of clonidine prevented the sympathetic initiation and aggravation of post-stenotic myocardial ischemia by a central nervous system action. This may be why clonidine is effective in exertional angina. Two other potential mechanisms by which alpha$_2$-adrenoreceptor activation can prevent myocardial ischemia have been described. Nathan & Feigl reported that alpha-adrenergic coronary vasoconstriction exerts a favourable effect on ischemic myocardium by preventing a transmural redistribution of blood flow away from the ischemic endocardium, a so-called anti-steal phenomenon.[67] In addition, Kitakaze demonstrated that intracoronary clonidine enhanced the vasodilatory effects of adenosine released from ischemic myocardium, thereby attenuating myocardial ischemia.[68]

Clonidine has been studied for management of peri-operative ischemia. Kent and co-workers [43] premedicated 23 cardiac surgery patients with 200 µg of clonidine or

placebo po. Ischemia was monitored from the time of premedication to cardiopulmonary bypass using leads II and V5. Patients receiving clonidine had decreased incidence and duration of ischemia compared with the placebo group. Quintin and colleagues reported the results of a study of 26 cardiac surgery patients who were premedicated with 2.5 $\mu g \cdot kg^{-1}$ clonidine or placebo po.[69] Ischemia was monitored from the time of premedication to bypass using leads II and V5. The cumulative duration of ST changes was decreased in the clonidine group. Recently, Dorman and co-workers evaluated the effect of clonidine on 43 patients undergoing coronary artery bypass surgery.[44] Oral clonidine (5 $\mu g \cdot kg^{-1}$) or placebo was administered pre-operatively and immediately prior to cardiopulmonary bypass. ST segments were analyzed continuously in leads II and V5. From sternotomy to aortic cross-clamping, the placebo group had a significantly increased incidence of ST depression when compared to the clonidine group. It was also shown that small, oral dose of clonidine reduces the incidence of myocardial ischemia in patients having vascular surgery.[70]

3.8. Aims of the study

New, more specific and selective alpha$_2$-adrenergic receptor agonists have recently been introduced for perioperative use to reduce anesthetic requirements and to provide hemodynamic stability in low-risk (ASA I-II) surgical patients.

The present series of investigations was initiated in order to gain information on the possible usefulness of the new alpha$_2$ agonists dexmedetomidine and mivazerol as anesthesia adjuvants in the perioperative period in patients with cardiovascular disease at risk for coronary artery lesions (*chapter 9*). Because information on the effects of dexmedetomidine and mivazerol on myocardial ischemia was limited, we initiated 5 laboratory investigations in dogs which were among the first to study the effects of dexmedetomidine and mivazerol on the coronary circulation and on the ischemic myocardium. We wanted to gain more information about possible mechanisms for the potential anti-ischemic effects of these new alpha$_2$ agonists.

More specifically, these investigations were designed:

- to assess the central sympatholytic effect and the peripheral vasoconstrictive effect of dexmedetomidine and to assess whether the systemic and coronary vasoconstriction of dexmedetomidine can be overcome by a calcium-channel blocker (*chapter 4*).
- to investigate whether this peripheral vasoconstrictive effect of dexmedetomidine can be reversed by the purinoceptor agonist ATP and to investigate whether the effects of dexmedetomidine on cardiac function are secondary to the peripheral effects (*chapter 5*).
- to study the balance between exogenous alpha$_2$-adrenergic and endogenous metabolic vasoregulation in normal myocardium and during reactive hyperemia, a situation when high endogenous purinergic substances like adenosine are present (*chapter 6*).

- to gain more information on the effect of dexmedetomidine and mivazerol on blood flow, metabolism and function of normal and ischemic myocardium, with special emphasis on the transmural distribution of myocardial blood flow (chapters 7 and 8).

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CHAPTER 4

Alleviation of the peripheral hemodynamic effects of dexmedetomidine by the calcium channel blocker isradipine

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ABSTRACT

Background: Alpha$_2$-adrenergic agonists have peripheral vasoconstrictive effects and central sympatholytic and sedative effects. Whereas the latter are the basis of their use in anesthesia, the former could limit their clinical application.
Methods: To study whether a vasodilator could alleviate the systemic and coronary vasoconstrictor effects of dexmedetomidine without influencing the central sympatholytic effects, the calcium-channel blocker isradipine was infused after a high dose of dexmedetomidine in anesthetized dogs.
Results: Dexmedetomidine 10 μg · kg^{-1} decreased plasma concentrations of norepinephrine and epinephrine by more than 90%, heart rate by 39%, cardiac output by 64%, dp/dt_{max} by 29% and increased mean arterial pressure by 55% and the left ventricular end-diastolic pressure 4-fold as compared to baseline. In addition, coronary blood flow decreased by 52% and coronary venous oxygen saturation by 51%. Isradipine could completely antagonize all the coronary and systemic hemodynamic changes induced by dexmedetomidine, but only partially the increase in LVEDP. Isradipine caused no changes in plasma catecholamine levels.
Conclusion: Isradipine could alleviate the peripheral hemodynamic actions of dexmedetomidine while having no effect on it's central sympatholytic properties.

Key words: alpha$_2$-adrenergic agonists -dexmedetomidine - calcium channel blockers - isradipine - cardiac function

INTRODUCTION

Alpha$_2$-adrenergic receptor agonists, as novel anesthetic agents, have been shown to have multiple beneficial effects in the perioperative period. These include improved hemodynamic stability, sedation, and a reduction in the anesthetic and analgesic requirements.[1] These effects are related to activation of pre-synaptic alpha$_2$-adrenergic receptors in the central nervous system with a reduction in norepinephrine release from adrenergic neurons. Drugs that activate these central alpha$_2$-receptors also demonstrate useful antihypertensive effects.[2] Paradoxically, although alpha$_2$-adrenergic agonists are centrally acting anti-hypertensive agents, activation of peripheral post-synaptic alpha$_2$-adrenergic receptors may include intense vasoconstriction,[3] especially after rapid intravenous bolus administration. This pressor effect could

cause coronary vasoconstriction and thus seriously limit the utility of these drugs. Therefore, if peripheral vasoconstriction would occur after the administration of alpha$_2$ agonists, a drug that could rapidly antagonize this vasoconstriction while preserving the central actions of alpha$_2$ agonists could be useful. Calcium channel blockers, widely used as antihypertensives and antiarrhythmics in cardiovasular therapy, could perhaps be administered for this purpose. The action of these drugs is attributed to a selective inhibition of the calcium influx into the cardiac and smooth muscle cells, which results in vascular smooth muscle relaxation and vasodilation, inhibition of cardiac automaticity and conduction and a reduction of myocardial contractility.[4] It has previously been shown that alpha$_2$-adrenoreceptor-mediated vasoconstriction could be antagonized by calcium channel blockers and is therefore primarily attributed to the facilitated influx of extracellular calcium ions.[5,6]
However, few studies have been published on the hemodynamic interactions of calcium-channel blockers and alpha$_2$ agonists.[7,8] Bloor and colleagues studied the effect of nifedipine infusion after dexmedetomidine 20 $\mu g \cdot kg^{-1}$ in isoflurane-anesthetized dogs.[8] However, these investigators did not study the effects of dexmedetomidine and nifedipine on the coronary blood flow.

The present investigation was designed to study whether isradipine, a calcium channel blocker with low lipid solubility and little negative inotropic effect,[9-11] is effective in alleviating the systemic and coronary hemodynamic effects of dexmedetomidine in halothane-anesthetized dogs.

METHODS

Anesthesia and Instrumentation

The studies were approved by the Local Animal Care Committee.
Eight mongrel dogs of either sex, weighing 29.7 ± 1.7 kg (range 23 -34 kg; mean ± SEM) were premedicated with 10 $\mu g \cdot kg^{-1}$ fentanyl IM. Anesthesia was induced 30 minutes later with thiopental. The dose of thiopental required to produce unconsciousness was 18.4 ± 1.7 $mg \cdot kg^{-1}$ (mean ± SEM). The dogs were intubated and mechanically ventilated to normocapnia with halothane and 67% nitrous oxide in oxygen. ECG electrodes were placed, and catheters for fluid administration and injection/infusion of drugs were inserted into the femoral vein, and into the superior vena cava through the right external jugular vein. Two 7F Millar microtransducer-tipped catheters were placed via a femoral artery, one in the central aorta and one in the left ventricle. A Swan-Ganz oximetric catheter (Edwards Oximetry TD Catheter 93A/731H) was floated into the pulmonary artery via the right external jugular vein. The chest was entered through a left thoracotomy incision; the heart was exposed, and an electromagnetic 2 or 2.5 mm blood flow sensor (Skalar transflow 601 system, Module MDL 400) was placed around the left anterior descending coronary artery. A small catheter for blood sampling was placed in the accompanying coronary vein. After instrumentation was completed, halothane was discontinued, and nitrous oxide

was supplemented as needed by additional fentanyl. The animals were allowed to stabilize for at least 30 minutes. No muscle relaxants were used, and no additional fentanyl had to be given after beginning the experimental protocol.

Measurements

ECG, heart rate (HR), phasic and mean arterial blood pressure (MAP), left ventricular pressure (LVP) and its first derivative (dP/dt_{max}), left ventricular end-diastolic pressure (LVEDP), phasic and mean flow in the left anterior descending coronary artery (CBF), and oxygen saturation in the pulmonary artery (S_vO_2) were measured continuously. Pressures were transduced and amplified with Philips amplifiers PR9330; S_vO_2 was determined and recorded continuously with an Edwards SAT 1 combined cardiac output and O_2 saturation computer and recorder. MAP, LVP, dP/dt, LVEDP, CBF, and ECG were recorded continuously on a Schwarzer 10 channel RE 412 recorder. Cardiac output (CO) was determined in triplicate at the various measuring points by thermodilution, and arterial, mixed venous, and coronary venous blood samples were drawn at the same times for immediate determination of blood gases (ABL 3 Radiometer), oxygen saturation, and hemoglobin (OSM 2 Radiometer, calibrated for dog blood). Blood samples taken at baseline (BL), after 1 and 10 $\mu g \cdot kg^{-1}$ dexmedetomidine and after isradipine were also prepared for later determination of plasma catecholamines (arterial blood only) by HPLC.[12] Systemic vascular resistance (SVR), coronary vascular resistance (CVR) [calculated as (MAP-LVEDP)/CBF], arterial, mixed venous, and coronary venous oxygen contents, systemic and regional myocardial oxygen extraction [(arterial minus mixed venous) and (arterial minus coronary venous) oxygen contents, respectively], were calculated.

Experimental protocol

After BL measurements were taken, dexmedetomidine was given intravenously in increasing cumulative doses of 0.1, 0.3, 1.0, 3.0, and 10 $\mu g \cdot kg^{-1}$. Each dose was given over one minute. After the last dose of dexmedetomidine, isradipine was infused for approximately 15 minutes at a rate sufficient to restore and maintain MAP at BL levels. Hemodynamic measurements and blood samples (as described below) were taken as follows: at BL; at the peak MAP response after each dose of dexmed; at equilibrium during the infusion of isradipine, and 30 and 60 minutes after discontinuation of isradipine.

Statistical Analysis

All data are expressed as mean ± SEM. The entire series of sampling points for all hemodynamic variables was analyzed by means of General Linear Model Analysis of Variance, and differences between individual points were identified by the Fisher's Least Squares Deviation test. As the catecholamine data were not normally distrib-

uted, the non-parametric Friedman test was used, with individual point di
detected by the Wilcoxon signed rank test. $P < 0.05$ was considered signifi

RESULTS

The peak increase in MAP occurred within one minute of the dexmede
administration. Times between the different doses of dexmedetomidine rar
6 to 11 minutes, due to minor variations in time necessary to take the hem
measurements and the blood samples. Isradipine was started 6.5 ± 0.6 min
the last dose of dexmedetomidine. The dose of isradipine required to retur
BL values was 0.86 ± 0.18 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Isradipine measurements were p
at 8 ± 1.5 minutes after the start of the infusion.

Hemodynamic Effects

There was no significant change from BL levels in any variable after the
(0.1 $\mu g \cdot kg^{-1}$) of dexmedetomidine. The effects of subsequent doses are

Table. *Hemodynamic effects of dexmedetomidine and isradipine*

	BL	DM 0.3	DM 1	DM 3	DM 10	ISRA INF	ISRA OFF 30'
HR	140 ± 11	123 ± 10	99 ± 6*+	92 ± 10*	86 ± 11*	120 ± 7+	102 ± 7*
MAP	109 ± 7	133 ± 7*	150 ± 7*	157 ± 6*	169 ± 10*	98 ± 6+	106 ± 4
CO	4.9 ± 0.5	4.4 ± 0.5	3.1 ± 0.3*	2.4 ± 0.3*	1.8 ± 0.2*	4.9 ± 0.5+	3.1 ± 0.5*
SVR	1916 ± 228	2566 ± 244	4128 ± 191*+	5549 ± 381*+	7727 ± 435*+	1769 ± 257+	3112 ± 439*
LVEDP	5.1 ± 0.9	9.2 ± 2.1*	13.3 ± 0.8*+	16.7 ± 1.8*+	21.6 ± 2.2*+	10.1 ± 1.0*+	8.1 ± 1.0
dP/dtmax	1993 ± 140	1929 ± 154	1807 ± 149	1593 ± 152	1414 ± 100*	1657 ± 116	1600 ± 114
CBF	40 ± 5	33 ± 7	26 ± 7*	23 ± 8*	19 ± 9*	44 ± 8+	36 ± 7
CVR	3.2 ± 0.7	5.5 ± 1.4	10.9 ± 3.6*	13.4 ± 5.3*	23.5 ± 7.5*+	2.7 ± 0.6+	3.7 ± 0.9
(A-V) O2Cont	5.0 ± 0.7	6.3 ± 0.8	7.3 ± 0.7*	9.2 ± 0.8*+	11.6 ± 1.0*+	4.1 ± 0.8+	6.8 ± 0.8*
Ven O2 Sat	75 ± 3	72 ± 3	70 ± 3*	63 ± 2*+	56 ± 3*+	82 ± 2+	72 ± 3+
(A-CV) O2Cont	14.9 ± 1.3	17.3 ± 1.5*	20.1 ± 0.9*+	20.2 ± 1.4*	22.2 ± 0.8*+	11.4 ± 1*+	15.5 ± 1.3+
Cor O2 Sat	31 ± 4	25 ± 4	20 ± 3	19 ± 4*	16 ± 4*	56 ± 3*+	39 ± 5*+

* = significantly different from baseline value; + = significantly different from preceding valu
Abbreviations: BL = baseline; DM = dexmedetomidine in $\mu g \cdot kg^{-1}$; Isra = isradipine; inf = infu
heart rate in $beats \cdot min^{-1}$; MAP = mean arterial pressure in mmHg; CO = cardiac output in $L \cdot r$
systemic vascular resistance in $dyne \cdot s \cdot cm^{-5}$; LVEDP = left ventricular end-diastolic pressu
dP/dtmax = first derivative of LV pressure in $mmHg \cdot s^{-1}$; CBF = coronary blood flow in $ml \cdot n$
coronary vascular resistance in $mmHg \cdot ml^{-1} \cdot min^{-1}$;(A-V) O_2Cont = arterial - mixed venous oxy
in $ml \cdot dl^{-1}$; Ven O_2 sat = mixed venous oxygen saturation in %; (A-CV) O_2Cont = arterial -coro
oxygen content in $ml \cdot dl^{-1}$; Cor O_2 sat: regional coronary venous oxygen saturation in %; Isra
min after discontinuation of isradipine; Isra off 60' = 60 min after discontinuation of isradipin

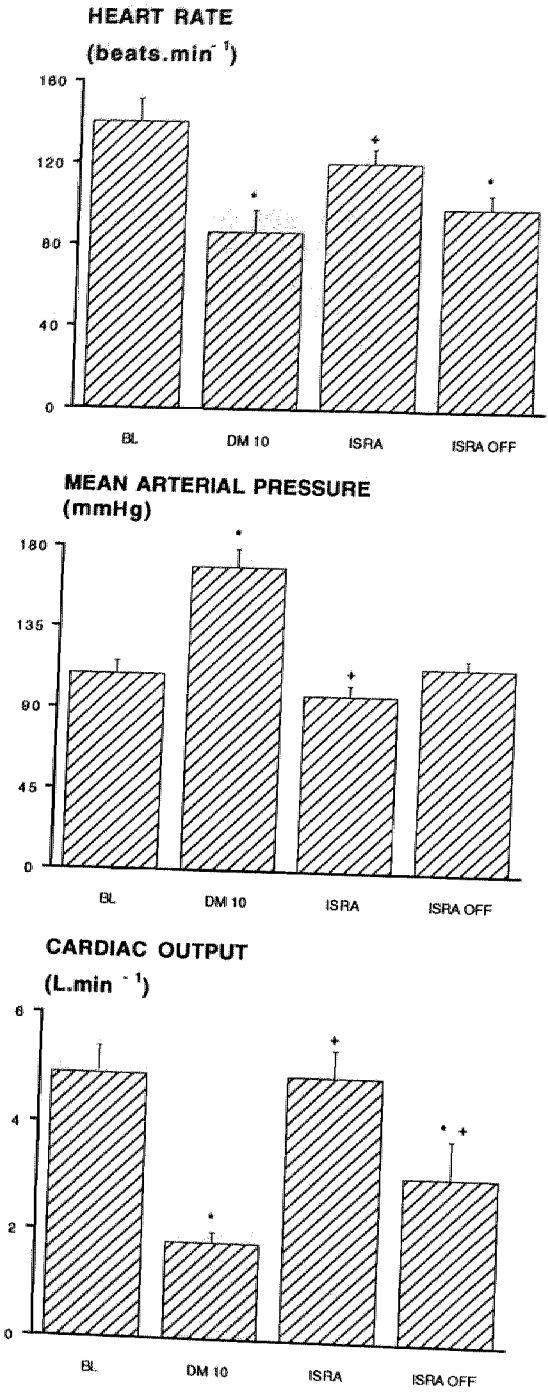
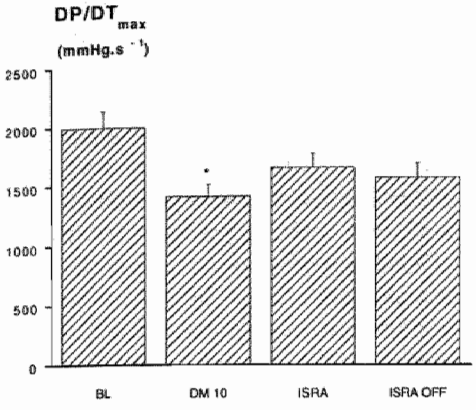
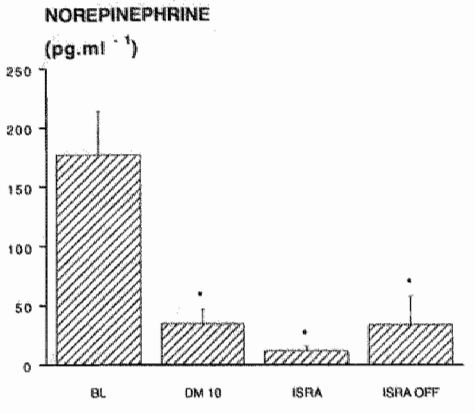
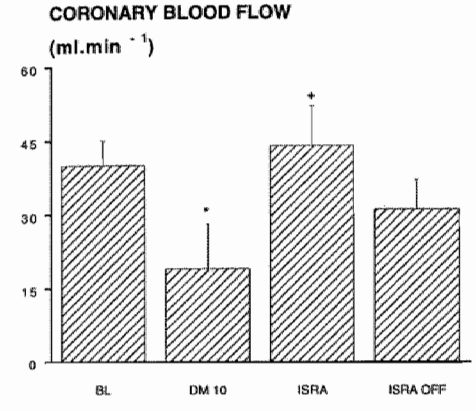


Figure 1. *Heart rate, mean arterial pressure and cardiac output*
mean ± sem data; n = 8; * = significantly different from BL value ($P < 0.05$); + = significantly different from preceding value ($P < 0.05$); Abbreviations: BL = baseline; DM 10 = dexmedetomidine 10 $\mu g \cdot kg^{-1}$; ISRA = isradipine 0.86 ± 0.18 $\mu g \cdot kg^{-1} \cdot min^{-1}$; ISRA OFF = 60 min after discontinuation of isradipine infusion







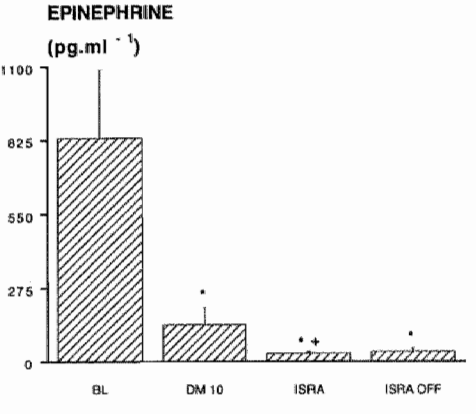


Figure 2. *DP/dTmax and coronary blood flow*
mean ± sem data; n = 8; * = significantly different from BL value ($P < 0.05$); + = significantly different from preceding value ($P < 0.05$); Abbreviations: BL = baseline; DM 10 = dexmedetomidine 10 $\mu g \cdot kg^{-1}$; ISRA = isradipine 0.86 ± 0.18 $\mu g \cdot kg^{-1} \cdot min^{-1}$; ISRA OFF = 60 min after discontinuation of isradipine infusion

Figure 3. *Plasma levels of norepinephrine and epinephrine*
mean ± sem data; n = 8; * = significantly different from BL value ($P < 0.05$); + = significantly different from preceding value ($P < 0.05$); Abbreviations: BL = baseline; DM 10 = dexmedetomidine 10 µg·kg-1; ISRA = isradipine 0.86 ± 0.18 µg·kg-1·min-1; ISRA OFF = 60 min after discontinuation of isradipine infusion

the Table and in Figure 1,2 & 3. All hemodynamic factors were changed significantly by the 1 $\mu g \cdot kg^{-1}$ and higher doses of dexmedetomidine.

Systemic circulation. There was a progressive, dose-related decrease in HR and increase in MAP from BL levels; after the last dose of dexmedetomidine these were 61% and 155% of BL respectively. Cardiac output decreased progressively to 36% of BL after last dose, and LVEDP increased concurrently to 424% of BL. SVR rose 4-fold. DP/dt_{max} tended to decrease, but the change was not significant until after the

last dose (10 μg · kg^{-1}) of dexmedetomidine. As CO fell, a compensatory doubling of systemic oxygen extraction occurred, resulting in a 30% decrease in mixed venous oxygen saturation. Within minutes after the start of the isradipine infusion, all systemic hemodynamic variables returned to BL levels, except LVEDP, which remained elevated compared to BL. Systemic oxygen extraction decreased to BL concomitantly.
After discontinuation of the 15 min infusion of isradipine, most of the dexmedetomidine-mediated actions on the systemic circulation were no longer present: MAP, LVEDP and dP/dt_{max} were similar to BL, the SVR was more than halved and the CO almost doubled as compared to the same values after DM 10 μg · kg^{-1}.

Coronary Circulation. After increasing doses of dexmedetomidine, CBF declined and CVR rose progressively. After the highest dose these were 48% and 734% of BL, respectively. Myocardial oxygen extraction [$(A\text{-}CV)O_{2Cont}$] increased from 14.9 ml ± 1.3 ml · dl^{-1} at BL to 22.2 ± 0.8 ml·dl^{-1} after the 10 μg · kg^{-1} dose. Within minutes after the start of the isradipine infusion, all coronary hemodynamic variables returned to BL levels. Regional myocardial oxygen extraction even declined to less than BL values.
After discontinuation of isradipine, most of the coronary vascular effects of dexmedetomidine were no longer apparent.

Changes in plasma catecholamines

BL levels of plasma norepinephrine and epinephrine were 177 ± 37 and 833 ± 256 pg · ml^{-1}, respectively. Dexmedetomidine decreased plasma concentrations of both catecholamines gradually and significantly. Isradipine did not change plasma catecholamine levels (figure 3).

DISCUSSION

The present study demonstrates that isradipine can reverse all the systemic and coronary hemodynamic effects of dexmedetomidine, except the effect on the LVEDP, without affecting dexmedetomidine's sympatholytic effect.

Hemodynamic effects of dexmedetomidine

The results on the systemic and coronary hemodynamic effects of dexmedetomidine in the present study were consistent with previous studies.[13-16] Dexmedetomidine decreased heart rate, cardiac output, dP/dt_{max}, coronary blood flow, and the circulating level of plasma catecholamines and increased mean arterial pressure, LVEDP and the systemic and coronary vascular resistance.
These results can be explained by activation of central $alpha_2$-adrenoreceptors, causing a reduction in sympathetic drive,[17-18] a presynaptically induced decrease in

norepinephrine release at the sympathetic neuron terminals, and activation of post-synaptic alpha$_2$-adrenergic receptors on vascular smooth muscle cells.[3]
Reduction of cardiac output has been reported for most alpha$_2$-adrenergic agonists.[19-22] There are several possible reasons for the decrease in cardiac output, including a reduction in heart rate, an increase in afterload,[19] coronary vasoconstriction with reduction of oxygen delivery[13] as well as a decrease in sympathetic tone. No direct negative inotropic effects from dexmetomidine have been observed in isolated canine hearts[23] or in ferret papillary muscle.[24]

In the present study, sequential doses of dexmedetomidine were administered to the same animals. A potential limitation of this experimental design is that we were not able to study drug-related effects versus time-related effects. Nevertheless, previous studies have already shown that, in dogs, most of the peripheral vasoconstrictive effects of lower doses of dexmedetomidine (0.5-1 $\mu g \cdot kg^{-1}$) disappear quickly within minutes after its administration, while the central sympatholytic effects remain much longer.[13, 25] Higher doses of dexmedetomidine (5 $\mu g \cdot kg^{-1}$) cause prolonged vasoconstriction for several hours.[8]

Peripheral vasoconstrictive effects may thus dominate the central effects under such circumstances as high dosage, initially following a rapidly given intravenous bolus and when the pre-existing sympathetic tone is low and not much room is available for the central sympatholytic effects of these drugs.[19,25,26] Because we wanted to study the vasodilatory effects of isradipine, we created such a vasoconstrictive condition in the present study: a high dose of 10 $\mu g \cdot kg^{-1}$ dexmedetomidine was rapidly administered in anesthetized dogs, a model known to exert powerful alpha-adrenergic vasoconstriction.[8, 20]

Isradipine-induced vasodilation

The calcium channel blocker isradipine has been used for treatment of hypertension.[27] The decrease in blood pressure after the administration of calcium channel blockers is probably due to relaxation of the vascular smooth muscle, secondary to decreased entry of calcium into the cell via voltage-dependent channels,[28,29] the same channel which is involved in transmission of the vasoconstrictive signal from alpha2 adrenergic receptor activation.[5,6] In the present experiment, isradipine could completely antagonize the vasoconstrictive effects of dexmedetomidine. This indicates that calcium influx plays a major role in dexmedetomidine's mediated vasoconstriction, as was previously shown for other alpha$_2$ agonists.[30] In the present experiment, the reduction in cardiac output after dexmedetomidine could be restored by isradipine. Because isradipine is a powerful systemic as well as coronary vasodilator, and also because isradipine, probably by baroreceptor activation, increased heart rate, our experiments do not permit a firm conclusion as to the cause of the restoration of cardiac output. Although isradipine decreased cardiac afterload and increased coronary perfusion, there was still a reduction in cardiac function after the administration of isradipine, as expressed by the increased LVEDP. The decrease in central sympathetic outflow from the central nervous system therefore appears to be

also an important mechanism for the decrease in cardiac function after dexmedetomidine.

When discussing interactions between alpha$_2$-adrenergic agonists and calcium channel blockers, it should be acknowledged that the hypnotic-anesthetic action of alpha$_2$ agonists is influenced by the activation/gating of central calcium channels.[31] Calcium channel blockers therefore seem to facilitate the hypnotic-anesthetic effect of dexmedetomidine.[31]

Extrapolation to humans

There is strong evidence to suggest a species-dependent heterogeneity of alpha$_2$-adrenoreceptors.[8,32] There also appear to be species differences in the cardiovascular effects of alpha$_2$- adrenorececeptor agonists. Alpha$_2$-adrenoreceptor agonists in dogs have been shown to result in an increase in blood pressure which is not followed by a decrease as occurs in humans. This would suggest that stimulation of the canine and human vascular alpha$_2$-adrenoreceptor does not produce the same result. That is, in dogs a lengthy period of vasoconstriction occurs such that the centrally-mediated reduction in sympathetic tone does not result in reduced blood pressure.[8, 19, 25] The overall effect in humans is a centrally mediated lowering of the blood pressure with a decrease in heart rate.[20] However, the administration of dexmedetomidine in human volunteers caused a biphasic hemodynamic response: the rapid (2 min) intravenous administration of dexmedetomidine 1 and 2 $\mu g \cdot kg^{-1}$ produced a transient increase in MAP, having a peak effect at 3 min and lasting approximately 11 min, whereas the systemic vascular resistance doubled. Thereafter, MAP remained below baseline levels for at least 5 hours.[20] Presently, it is generally accepted that a continuous infusion of alpha$_2$ agonists might prevent this initial pressor phase and is perhaps the more appropriate way for administering these drugs to humans.[33,34] Nevertheless, the present investigation not only showed that isradipine was able to reverse the peripheral hemodynamic effects of dexmedetomidine, but also that, after stopping the 15 min infusion of this short-acting calcium channel blocker, most of the initial hemodynamic side-effects of dexmedetomidine had already dissipated. Alpha$_2$-adrenoreceptor agonists, as anesthetic adjuvants, appear to be especially beneficial in the high-risk cardiovascular population, because of their central sympatholytic and hemodynamic stabilizing properties.[34] If peripheral, potentially undesirable, vasoconstrictive effects of alpha$_2$ agonists would occur initially after their administration, the present study indicates that the short-lasting administration of a short-acting calcium antagonist like isradipine could probably be used to rapidly antagonize these vasoconstrictive effects, while having no effect on the central sympatholytic and anesthetic qualities of the alpha$_2$ agonist.[31] More investigations in humans are necessary to further study these interactions between alpha$_2$ agonists and calcium channel blockers.

The authors conclude that isradipine could alleviate the peripheral, potentially undesirable, hemodynamic actions of dexmedetomidine while having no effect on it's central sympatholytic properties.

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CHAPTER 5

Reversal of the systemic and coronary vasoconstrictive effects of dexmedetomidine by the purinoceptor agonist ATP

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ABSTRACT

The specific alpha$_2$-adrenoreceptor agonist dexmedetomidine has central sympatholytic and peripheral vasoconstrictive effects. Dexmedetomidine can cause coronary vasoconstriction and can reduce cardiac function. We investigated whether these two effects can be blocked or reversed by the purinoceptor agonist ATP and by the alpha$_2$-adrenoreceptor antagonist atipamezole.

In halothane-anesthetized dogs, two sequential doses of 2 $\mu g \cdot kg^{-1}$ dexmedetomidine decreased heart rate, cardiac output, and dP/dt_{max} and increased mean arterial pressure, left ventricular end-diastolic pressure (LVEDP) and the systemic and coronary vascular resistance. After the first dexmedetomidine dose, coronary blood flow decreased by 54% and myocardial oxygen extraction increased by 28%. Cardiac function, expressed as the ratio of left ventricular stroke work (LVSW) and LVEDP, decreased by approximately 50% while the plasma concentration of norepinephrine decreased as well. ATP infusion (0.74 and 2.20 $mg \cdot kg^{-1} \cdot min^{-1}$ after the first and the second dose of dexmedetomidine, respectively) restored LVEDP, systemic vascular resistance and systemic oxygen extraction to baseline values and increased coronary blood flow by 170% compared to baseline, which resulted in a 60% drop in myocardial oxygen extraction. The LVSW/LVEDP ratio however recovered only partially while plasma catecholamine levels remained below baseline values. Atipamezole reversed systemic and coronary hemodynamic variables as well as plasma catecholamines to baseline values.

Since the administration of ATP only partially reversed the reduction in cardiac function induced by dexmedetomidine, the authors conclude that the reduction in cardiac function is mainly due to dexmedetomidine's sympathetic inhibitory effect rather than to it's peripheral vasoconstrictive effect.

Key words: Alpha$_2$-adrenergic agonists, dexmedetomidine, ATP, atipamezole, cardiac function

INTRODUCTION

Previous studies have demonstrated the ability of alpha$_2$-adrenergic agonists to alter systemic hemodynamics by activation of alpha$_2$-adrenergic receptors in the brain.

This results in diminished sympathetic tone and a decrease in arterial blood pressure and heart rate.[31] Stimulation of these receptors in the central nervous system also produces a sedative-hypnotic effect and reduces the requirements for anesthetics and analgesics during general anesthesia. Therefore, these agents possess useful properties as adjuncts for general anesthesia.[18]

However, a potential problem might be the concomitant peripheral vasoconstriction by postsynaptic alpha$_2$-adrenoreceptor stimulation. Activation of these peripheral alpha$_2$-adrenergic receptors may result in significant alterations in systemic and coronary hemodynamics.[4,12,13,24] Studies on the effects of dexmedetomidine, a highly selective alpha$_2$-adrenoreceptor agonist,[6,27,32] on coronary blood flow yielded conflicting results. Savola et al found no effect of dexmedetomidine on coronary blood flow using positron emission tomography in enflurane-anesthetized dogs.[25] Schmeling and coworkers also reported no change in coronary blood flow after dexmedetomidine in awake dogs.[28] In contrast, Flacke and colleagues reported a transient reduction of approximately 20% in coronary blood flow in enflurane-anesthetized dogs.[10] Studies in halothane-anesthetized dogs in our laboratory also showed a significant reduction of myocardial blood flow.[20]

Dexmedetomidine, like other alpha$_2$ agonists, causes diminished cardiac function.[1,3,7,21] It was shown that dexmedetomidine had no direct myocardial depressant effect, either in isolated papillary muscles[15] or in the isolated canine heart.[9] Two possible explanations for the diminished cardiac function after alpha$_2$ agonists have been raised, none of which are fully supported by previous studies. The sympatholytic action of alpha$_2$ agonists could induce a reduction in cardiac function, but this does not explain why a diminished cardiac function was observed in autonomically blocked dogs.[8] Flacke and coworkers suggested that limited myocardial oxygen supply due to coronary vasoconstriction could lead to decreased cardiac function.[8] If so, it is not clear why no reduction in cardiac function was found in isolated, blood perfused, dog hearts.[9] Therefore, these theories require further investigation.

The present experiments were designed to evaluate whether the systemic and coronary vasoconstriction of dexmedetomidine could be corrected by the purinoceptor agonist ATP, a potent vasodilator,[11,23,30] and whether the observed changes in cardiac function, could be explained by changes in myocardial oxygen extraction and/or plasma catecholamine levels.

MATERIAL AND METHODS

General Preparation

The studies were approved by the local animal care committee.
Eight mongrel dogs of either sex, weighing 29.4 ± 1.3 kg (range 24-36) (mean ± SEM) were premedicated with fentanyl 10 $\mu g \cdot kg^{-1}$ IM. Anesthesia was induced 40 min later with thiopental. The dose required for unconsciousness was 16 ± 1.4 $mg \cdot kg^{-1}$ (mean ± SEM). The dogs were intubated and mechanically ventilated to

normocapnia with halothane and 67% nitrous oxide in oxygen. During the subsequent surgical preparation, supplemental fentanyl and/or thiopental were given as needed to maintain surgical anesthesia. Total supplemental doses were 4.1 ± 2.4 $\mu g \cdot kg^{-1}$ and 4.3 ± 2.0 $mg \cdot kg^{-1}$, respectively (mean ± SEM). ECG electrodes were placed, and catheters for fluid administration and injection/infusion of drugs were inserted into the femoral vein, and into the superior vena cava via the right internal jugular vein. Two 7F Millar microtransducer-tipped catheters were placed via a femoral artery, one in the central aorta and one in the left ventricle. A Swan-Ganz oximetric catheter (Edwards Oximetry TD Catheter 93A/731H) was floated into the pulmonary artery through the right internal jugular vein. The chest was entered through a left thoracotomy incision; the heart was exposed, and an electromagnetic 2 or 2.5 mm blood flow sensor (Skalar transflow 601 system, Module MDL 400) was placed around the left anterior descending coronary artery. A small catheter for blood sampling was introduced into the great cardiac vein and advanced retrogradely until it was positioned in the region to become ischemic. After instrumentation was discontinued, halothane administration was stopped, nitrous oxide was continued, and the animals were allowed to stabilize. No muscle relaxants were used. The experimental protocol was begun approximately 30 minutes later (131 ± 6 min after induction; mean ± SEM).

Measurements

ECG, heart rate, phasic and mean arterial blood pressure, left ventricular pressure and its maximal rate of rise ($LVdP/dt_{max}$), left ventricular end-diastolic pressure (LVEDP), phasic and mean flow in the left anterior descending coronary artery, and oxygen saturation in the pulmonary artery (S_vO_2) were measured continuously. Pressures were transduced and amplified with Philips amplifiers PR 9330 and S_vO_2 was determined and recorded continuously with an Edwards Sat 1 combined cardiac output and O_2 saturation computer and recorder. Mean arterial pressure, left ventricular pressure, $LVdP/dt_{max}$, LVEDP, coronary blood flow, and ECG were recorded continuously on a Schwarzer 10 channel RE 412 recorder. At each sampling point, cardiac output was determined by thermodilution in triplicate, and arterial, mixed venous and coronary venous blood samples were drawn at the same times (see experimental protocol). Blood gases (ABL 3 Radiometer), oxygen saturation and hemoglobin (OSM 2 Radiometer, calibrated for dog blood) were measured immediately in blood from all three sites. Plasma catecholamines were determined later by HPLC on arterial blood.[26] Systemic vascular resistance, coronary vascular resistance [(mean arterial pressure -LVEDP) · coronary blood $flow^{-1}$], arterial, mixed venous, and coronary venous oxygen contents [(Hb · 1.39 · saturation) + (PO_2 · .003)], systemic and myocardial oxygen extraction [(arterial - mixed venous) and (arterial-coronary venous) oxygen contents, respectively], and myocardial regional oxygen uptake (coronary blood flow · myocardial oxygen extraction) were calculated. The ratio of left ventricular stroke work (=systolic left ventricular pressure·stroke volume) and LVEDP was utilized as an index of cardiac function. Stroke volume was calculated as cardiac index/heart rate.

Experimental protocol

After baseline 1 measurements were taken, ATP was infused at a rate of 0.28 ± 0.05 $mg \cdot kg^{-1} \cdot min^{-1}$ for 5 min. After the measurements were performed, the infusion was stopped and 15 min was allowed for hemodynamic stabilization to a second baseline. Subsequently dexmedetomidine 2 $\mu g \cdot kg^{-1}$, dissolved in 20 ml saline, was administered slowly iv over 5 min. Measurements were repeated 15 min after the end of the administration. Thereafter, an infusion of ATP was given at a rate necessary to return cardiac output and LVEDP to baseline levels. When conditions were steady at this level, measurements were repeated, representing the effect of the combination of dexmedetomidine 2 $\mu g \cdot kg^{-1}$ plus ATP. One hour after the first dose of dexmedetomidine 2 µg·kg-1, a second dose of 2 µg·kg-1 dexmedetomidine was added slowly iv over 5 min while the ATP infusion was continued. To maintain cardiac output at baseline level, the rate of ATP infusion had to be adjusted. After measuring the effects of the combined dose of dexmedetomidine plus high dose ATP, the ATP infusion was discontinued and, 15 min after the end of the second dexmedetomidine administration, measurements were repeated, representing the effect of the two sequential doses of dexmedetomidine in the absence of ATP.
Finally, atipamezole, a specific pharmacological $alpha_2$ antagonist, was given in a bolus dosis of 0.15 $mg \cdot kg^{-1}$, and final measurements were taken at the time of peak blood pressure change. Since atipamezole antagonized also the central anesthetic-potentiating effect of dexmedetomidine, the level of anesthesia became noticeably lighter and some dogs began to move. In these cases, thiopental was given IV promptly prior to the post-atipamezole measurements.

Statistical analysis

The entire series of sampling points was analysed by means of GLM ANOVA, or by the non-parametric Friedman test if the data were not normally distributed. Differences between individual points were identified by the Fisher least significant difference (LSD) test. All data are expressed as mean ± SEM. $P < 0.05$ was considered significant.

RESULTS

Effect of ATP

ATP infusion increased heart rate, cardiac output, dP/dt_{max}, LVSW/LVEDP and decreased systemic vascular resistance and mean arterial pressure (table and figure 1 & 2). ATP also increased coronary blood flow and decreased myocardial oxygen extraction (figure 3). Fifteen minutes after the discontinuation of the ATP infusion, all measured parameters had returned to the first baseline values apart from the mean

Table. *Hemodynamic effects of ATP, dexmedetomidine, dexmedetomidine + ATP and dexmedetomidine + atipamezole*

	BL (1)	ATP 0.28	BL (2)	DM 2	DM 2 + ATP 0.74	DM 4 + ATP 2.20	DM 4	ATIPAM
HR	131 ± 9	170 ± 8*+	141 ± 9+	94 ± 8*+	112 ± 7*	101 ± 9*	90 ± 10*	171 ± 10*+
MAP	103 ± 7	86 ± 6*+	116 ± 8*+	120 ± 6*	92 ± 5*+	91 ± 5*#	115 ± 7*+	133 ± 11*+
LVEDP	5.6 ± 0.7	3.4 ± 0.6	5.3 ± 0.6	10.1 ± 2.3*	5 ± 0.8+	8.5 ± 1.4	11 ± 2.2*	7.6 ± 1.9+
dP/dt_{max}	1863 ± 89	2018 ± 113*+	1969 ± 116	1443 ± 62*+	1600 ± 68*	1588 ± 79*	1375 ± 80*	2025 ± 126+
SVR	2240 ± 339	1325 ± 122*+	2622 ± 374+	4855 ± 533*+	2262 ± 255+	2466 ± 309#	5234 ± 466*+	3237 ± 519*+
CVR	2.9 ± 0.6	1.2 ± 0.2	3.3 ± 0.7	12 ± 3.9*+	1.4 ± 0.3+	1.1 ± 02#	11.6 ± 4*+	3.4 ± 0.7+
VO2	4.6 ± 0.4	6.1 ± 0.6*+	4.9 ± 0.5	2.4 ± 0.6*+	4.9 ± 0.7+	4.4 ± 0.7#	2.4 ± 0.7*+	5.6 ± 1.3+
NEPI	150 ± 33	211 ± 47	150 ± 41	31 ± 7*+	47 ± 17*	24 ± 7*	16 ± 3*	207 ± 64+
EPI	333 ± 110	344 ± 115	392 ± 167	87 ± 40	99 ± 51	56 ± 24*	38 ± 15*	582 ± 381+

* = significantly different from baseline (1) value; + = significantly different from preceding value; # = significantly different from DM alone; mean ± sem data; n=8; $P < 0.05$; ATP in $mg \cdot kg^{-1} \cdot min^{-1}$; DM in $\mu g \cdot kg^{-1}$; DM 4 = DM 2 + 2. abbreviations: BL = baseline; DM = dexmedetomidine; atipam = atipamezole; HR = heart rate in beats·min-1; MAP = mean arterial pressure in mmHg; LVEDP = left ventricular end-diastolic pressure in mmHg; dP/dt_{max} = first derivative of LV pressure in $mmHg \cdot s^{-1}$; SVR = systemic vascular resistance in $dyne \cdot s \cdot cm^{-5}$; CVR = coronary vascular resistance in $mmHg \cdot ml^{-1} \cdot min^{-1}$; VO_2 = myocardial regional oxygen uptake in $ml \cdot min^{-1}$; NEPI = norepinephrine in $pg \cdot ml^{-1}$; EPI = epinephrine in $pg \cdot ml^{-1}$.

arterial pressure. Mean arterial pressure at baseline 2 was slightly, but significantly, higher than at baseline 1.

Effect of the first dose of DM

Administration of 2 $\mu g \cdot kg^{-1}$ dexmedetomidine decreased heart rate, cardiac output, and dP/dt_{max} and increased mean arterial pressure, LVEDP and the systemic and coronary vascular resistance (table and figure 1 & 2). Coronary blood flow decreased by 54% and myocardial oxygen extraction increased by 28% (figure 3). Cardiac function, expressed as the LVSW/LVEDP ratio decreased by approximately 50% while the plasma concentration of norepinephrine decreased as well.

Effect of the first dose of DM in combination with ATP

After these measurements had been performed, a second ATP infusion was begun and titrated to attain hemodynamic conditions close to the pre-dexmedetomidine baseline. These were in fact realized for cardiac output, LVEDP, systemic vascular resistance and systemic oxygen extraction. LVSW/LVEDP was fully restored as was mixed venous oxygen saturation. The infusion rate of ATP required was 0.74 ± 0.1 $mg \cdot kg^{-1} \cdot min^{-1}$. Changes in heart rate, dP/dt_{max}, and plasma catecholamines were not significant. Coronary blood flow increased five fold compared to the pre-ATP timepoint, and there was an increase of 123% compared to baseline. Myocardial oxygen extraction was decreased accordingly.

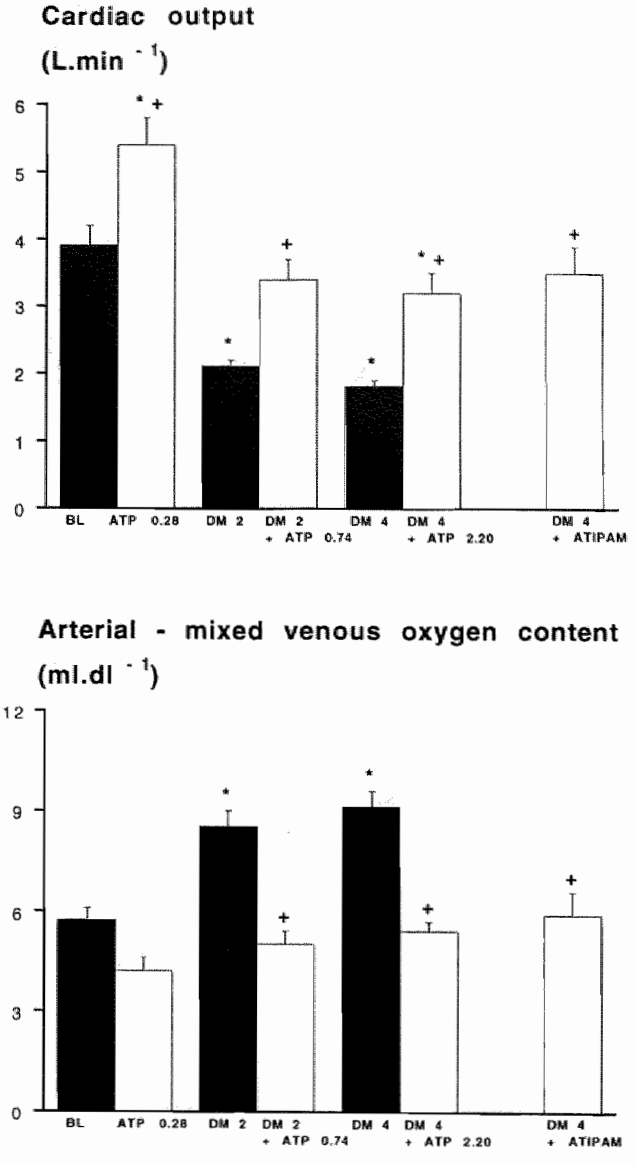

Figure 1. *Cardiac output (upper) and arterial -mixed venous oxygen content (lower)*
mean ± sem data; n = 8; * = significantly different from BL value ($P < 0.05$); + = significantly different from preceding BL or DM value ($P < 0.05$); abbreviations: BL = baseline; ATP = adenosine triphosphate; DM = dexmedetomidine; ATIPAM = atipamezole; DM in $\mu g \cdot kg^{-1}$; ATP in $mg \cdot kg^{-1} \cdot min^{-1}$; DM 4 = DM 2 + 2

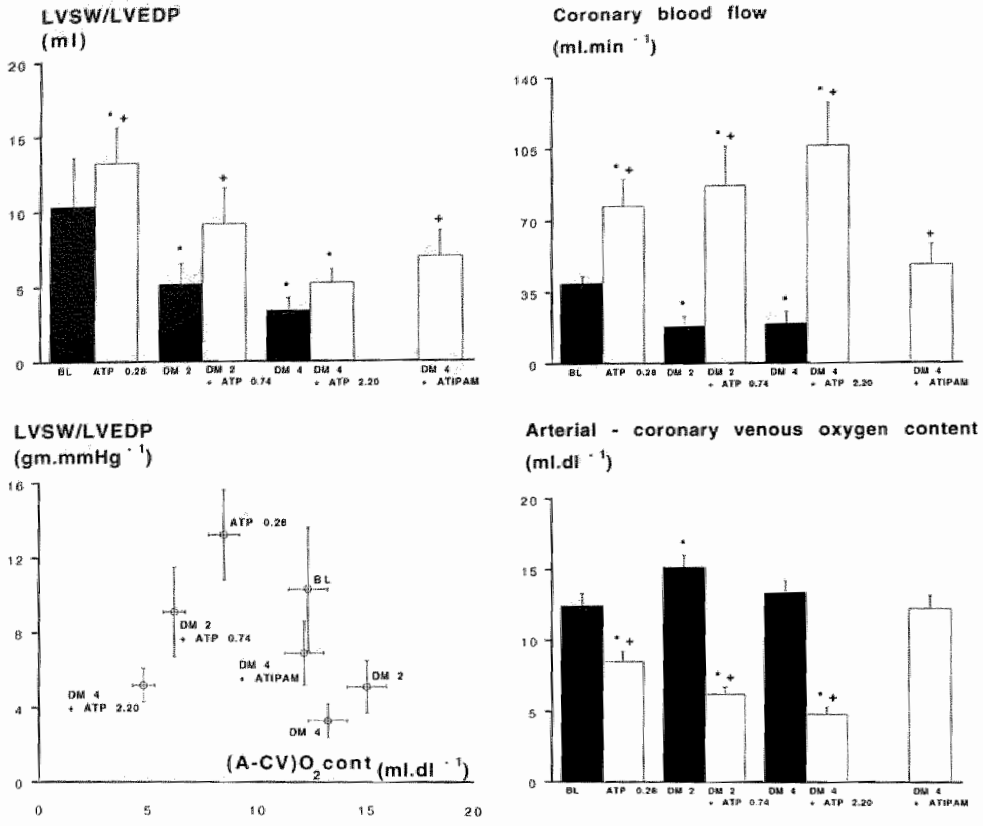

Figure 2. *Left ventricular stroke work / left ventricular end-diastolic pressure ratio (upper) and LVSW/LVEDP ratio plotted against the arterial - coronary venous oxygen content (lower)*
mean ± sem data; n = 8; * = significantly different from BL value ($P < 0.05$); + = significantly different from preceding BL or DM value ($P < 0.05$); Abbreviations: BL = baseline; ATP = adenosine triphosphate; DM = dexmedetomidine; ATIPAM = atipamezole; DM in µg·kg-1; ATP in mg·kg-1·min-1; DM 4 = DM 2 + 2

Figure 3. *Coronary blood flow (upper) and arterial-coronary venous oxygen content (lower)*
mean ± sem data; n = 8; * = significantly different from BL value ($P < 0.05$); + = significantly different from preceding BL or DM value ($P < 0.05$); Abbreviations: BL = baseline; ATP = adenosine triphosphate; DM = dexmedetomidine; ATIPAM = atipamezole; DM in µg·kg-1; ATP in mg·kg-1·min-1; DM 4 = DM 2 + 2

Effect of the first and second dose of DM in combination with ATP

When a second dose of 2 $\mu g \cdot kg^{-1}$ dexmedetomidine was given over 5 min, the ATP infusion rate had to be increased to 2.2 ± 0.3 $mg \cdot kg^{-1} \cdot min^{-1}$ in order to maintain near baseline conditions. This was achieved for LVEDP, systemic vasular resistance and systemic oxygen extraction. Heart rate, cardiac output and dP/dt_{max} were between baseline levels and the values seen during the first infusion of dexmedetomidine. Plasma epinephrine level was decreased and the plasma norepinephrine level tended to decrease even further. Regional coronary blood flow, however, increased still by another 21% compared to ATP alone and by 170% compared to baseline. This resulted in an even greater drop in myocardial oxygen extraction. At this time, regional myocardial oxygen consumption had returned to the baseline value. The LVSW/LVEDP ratio however remained significantly below baseline value, as did arterial catecholamine levels.

Effect of the first and second dose of DM

After discontinuation of the ATP infusion, the hemodynamic effects of dexmedetomidine reappeared. Heart rate, cardiac output, LVSW/LVEDP and dP/dtmax were slightly lower than after the first dose of dexmedetomidine, while systemic vascular resistance was slightly higher. Catecholamine levels decreased further to very low levels.

Effect of Atipamezole

The administration of the pharmacological antagonist atipamezole precipitated reversal to baseline levels of hemodynamic variables (cardiac output, LVEDP, dP/dt_{max}, LVSW/LVEDP, coronary blood flow, coronary vascular resistance, [Art-Ven] O_2, [Art-CorVen] O_2, regional myocardial VO_2) and plasma catecholamines. Heart rate and mean arterial pressure even increased above baseline values.

To illustrate a possible relationship between myocardial oxygen extraction and cardiac function, LVSW/LVEDP was plotted as a function of $(A\text{-}CV)O_2$ content differences (figure 2, lower pannel). Compared to the baseline situation, ATP caused a left upward shift and dexmedetomidine a right downward shift of the LVSW/LVEDP-$(A\text{-}CV)O_2$ content difference relation. Infusion of ATP after dexmedetomidine 2 $\mu g/kg^{-1}$ recovered LVSW/LVEDP to baseline levels, but at $(A\text{-}CV)O_2$ contents considerably below baseline. ATP infusion after the second dexmedetomidine dose did not recover LVSW/LVEDP even though $(A\text{-}CV)O_2$ content differences were even lower.

DISCUSSION

The results of the present investigation demonstrated that the potent vasodilator ATP could reverse the systemic and coronary vasoconstrictive effects of dexmedetomid-

ine, but could only partially restore parameters of reduced cardiac function to baseline values. On the other hand, atipamezole, which did not increase coronary blood flow but restored catecholamine plasma levels, improved parameters of cardiac function to baseline values.

Experimental set-up

In the present experiment, we wanted to make an attempt to determine whether the reduction in cardiac function after dexmedetomidine was secondary to it's peripheral vasoconstrictive effect. Therefore, we wanted to use a vasodilator lacking negative inotropic effects. To enable repetitive measurements with and without the vasodilator, a short-acting vasodilator was needed.
We recently observed that the vasoconstrictive effect of dexmedetomidine was abolished during reactive hyperemia, a condition mainly attributed to the vasodilatory effect of adenosine. Therefore, ATP, a short acting vasodilator lacking negative inotropic effects (table, figure 1 and figure 2) was chosen to reverse the vasoconstrictive effect of dexmedetomidine. ATP is an unspecific agonist on purinoceptors and may evoke vasorelaxation due to its own action on purinoreceptors or by triggering the release of nitric oxide.[16] As ATP is degraded via ADP and AMP to adenosisne via ecto-5'-nucleotidases with each step of degradation another powerful vasodilator is formed.

The overall cardiovascular effect of alpha$_2$ agonists is determined by the relative preponderance of central versus peripheral effects. It was shown that the clinical dose of Dexmedetomidine 1 $\mu g \cdot kg^{-1}$ decreased the plasma catecholamine levels and decreased heart rate, but had no effect on cardiac output or mean arterial pressure in anesthetized dogs.[20] Dexmedetomidine 3 $\mu g \cdot kg^{-1}$ also decreased cardiac output by 30 ± 6%, increased mean arterial pressure by 23 ± 10% and increased the systemic vascular resistance by 60 ± 9%.[22] After the high dose of dexmedetomidine 10 µg·kg-1, the vasoconstrictive effects of dexmedetomidine predominated: mean arterial pressure increased by 52 ± 7%, cardiac output decreased by 60 ± 8% and systemic vascular resistance increased by 256 ± 10%.[20]
For the study of the interaction between the vasodilatory effects of ATP and the vasoconstrictive effects of dexmedetomidine, we used a dose of dexmedetomidine 2 $\mu g \cdot kg^{-1}$. As mentioned above, in this dose range, alpha$_2$-adrenergic vasoconstriction was not maximal, but was associated with a significant increase in systemic vascular resistance and decrease in cardiac function and plasma catecholamines. The second infusion of dexmedetomidine, one hour after the first dose, was given to study the effects of ATP at even lower levels of circulating plasma catecholamines. Previous studies have shown that, in dogs, most of the peripheral vasoconstrictive effects of dexmedetomidine have disappeared one hour after its infusion, while the central sympatholytic effects remain for several hours.[2,10,28]

Atipamezole is a potent, selective and specific antagonist of both centrally and peripherally located alpha$_2$-adrenoreceptors, with an alpha$_2$/alpha$_1$ selectivity of 8526.[33,34] In previous studies, 600 $\mu g \cdot kg^{-1}$ atipamezole completely reversed the

hemodynamic effects of 10 μg·kg-1 dexmedetomidine,[20] while 150 μg·kg^{-1} atipamezole reversed the hemodynamic effects of 3 μg·kg-1 dexmedetomidine.[22] Therefore, we chose a dose of 150 μg·kg^{-1} of atipamezole to reverse hemodynamic parameters to baseline values after the second dose of dexmedetomidine.

Analysis of changes in cardiac function of the various combinations of these drugs is hampered by changes in preload and afterload, which are known to influence cardiac output and LV dP/dtmax. We used LVSW/LVEDP as an index of cardiac function, because it takes into account changes in various hemodynamic variables, such as stroke volume, blood pressure and LVEDP.

Purinoreceptor-induced vasodilation

In the present experimental preparation, ATP alone caused a fall in blood pressure with associated reflex baroreceptor activation. ATP increased heart rate, cardiac output, dP/dt_{max} and the LVSW/LVEDP ratio. While ATP restored systemic vascular resistance after dexmedetomidine to baseline values, it increased coronary blood flow significantly above baseline values. This indicates that the vasodilator effects of ATP are more pronounced in the coronary vessels than in the systemic vascular bed. While ATP restored systemic vascular resistance after dexmedetomidine to baseline values, it is possible that the distribution of cardiac output between the various organs was not the same as during baseline. Studies in our laboratory have shown that $alpha_2$-adrenergic vasoconstriction occurs non uniformly in various tissues,[19] whereas ATP-induced vasodilation is probably more uniformly distributed to all vascular beds.

While the intravenous administration of ATP is probably not readily applicable in the clinical situation, this study showed in any case that purinoreceptor-induced vasodilation can overcome the vasoconstrictive effects of $alpha_2$-adrenoreceptor activation. This finding is in agreement with previous studies on the effects of adenosine and reactive hyperemia on $alpha_2$-adrenoreceptor-mediated vasoconstriction.[14,20] Kitakaze and coworkers showed that $alpha_2$-adrenoreceptor activation by clonidine could enhance the vasodilatory effects of adenosine released from ischemic myocardium.[17] We previously reported that dexmedetomidine did not decrease blood flow in the endocardial and midmyocardial layers of the myocardium during reactive hyperemia.[20] A similar mechanism of overruling of adrenergic vasoconstriction by metabolic vasodilation could also be responsible for the absence of vasoconstriction in the inner layers of ischemic myocardium after the administration of dexmedetomidine or mivazerol.[21,22]

Effects of dexmedetomidine on cardiac function

Reduction of cardiac function has been reported for most $alpha_2$-adrenergic agonists, both in animals and in humans.[1,3,7,21]
The central sympatholytic action of $alpha_2$ agonists with a reduction in inotropic support might be an important contributive factor to the reduction in cardiac function.

This could be evidenced by the findings that dexmedetomidine had no direct myocardial depressant effect in isolated papillary muscles or in the isolated canine heart.[9,15] Flacke and coworkers suggested that limited myocardial oxygen supply due to coronary vasoconstriction could induce a decrease in cardiac function.[8]

In the present experiment, ATP infusion after dexmedetomidine 2 $\mu g \cdot kg^{-1}$ administration could restore LVSW/LVEDP to baseline values, with a coronary blood flow significantly higher and an oxygen extraction significantly lower than at baseline. However, under baseline conditions with normal resting coronary blood flow, ATP also increased LVSW/LVEDP to a similar extent as seen after dexmedetomidine 2 $\mu g \cdot kg^{-1}$. This indicates that it is not likely that the improvement in cardiac function after ATP is secondary to improved oxygen supply to the heart. Moreover, after the second dose of dexmedetomidine, ATP infusion increased coronary blood flow to very high values while the LVSW/LVEDP remained below the baseline value. So, despite potent vasodilation by ATP, cardiac function recovered only partially. Restoration of cardiac function to baseline was obtained with atipamezole, which did not increase coronary blood flow but which restored plasma catecholamine levels. Therefore, the decrease in sympathetic outflow from the central nervous system appears to be a more important mechanism for the decrease in cardiac function after dexmedetomidine than the limitation of oxygen supply.

The possibility of an ischemia-reducing effect of the ATP treatment in the present experiment is not likely. We have shown that doses of dexmedetomidine up to 10 $\mu g \cdot kg^{-1}$ decrease coronary blood flow without a change in oxygen or lactate extraction, indicating adequate adaptation of myocardial blood flow to metabolic requirements.[20]

Extrapolation to man

Because of their central sympatholyic and hemodynamic-stabilizing properties, alpha$_2$ agonists appear to be especially useful as anesthetic adjuvants in the high-risk cardiovascular patients undergoing major surgery.[5,7] Recent evidence suggests that dexmedetomidine, when administered perioperatively, may result in decreased risk for adverse cardiac events including myocardial ischemia.[29]

There is evidence to suggest that in dog the peripheral vasoconstrictive effects of alpha-adrenergic stimulation are more predominant as compared to humans.[2] Nevertheless, it is important to be able to reverse any possible peripheral vasoconstriction of alpha$_2$ agonists. The goal of the utilization of alpha$_2$ agonists in anesthesiology is to preserve the-desired-central actions of the drugs without incurring their peripheral-potentially undesirable- effects. The "antagonism" must be restricted to the periphery. It was previously shown that calcium-channel antagonists are effective in blocking alpha-adrenoreceptor induced vasoconstriction.[2] In the present experiment, we showed that a vasodilator like ATP could functionally reverse the systemic and coronary vasoconstrictor effects of dexmedetomidine.

Conclusions

The authors conclude that the potent vasodilator ATP can completely reverse the coronary vasoconstrictor effect of dexmedetomidine but only partially the reduction of cardiac function. The pharmacological antagonist atipamezole reversed the central as well as the peripheral effects of dexmedetomidine so that cardiac function and catecholamine levels returned to baseline. The reduction of cardiac function after dexmedetomidine therefore may be primarily attributed to the sympathetic inhibition and reduced plasma catecholamine levels and to some extent to peripheral effects.

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CHAPTER 6

Coronary vascular effects of dexmedetomidine during reactive hyperemia in the anesthetized dog

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Coronary vascular effects of dexmedetomidine during reactive hyperemia in the anesthetized dog

ABSTRACT

Objective: The central sympatholytic effect of alpha$_2$-adrenergic agonists is believed to be beneficial during myocardial ischemia, but the peripheral vasoconstrictive effect is controversial. The aim of this study was to investigate the coronary vascular effects of dexmedetomidine (DM) during reactive hyperemia.
Design: The study had a prospective, randomized, open comparative design.
Setting: University animal laboratory.
Participants: Nine mongrel dogs.
Interventions: Coronary artery occlusions lasting 2 min were induced 5 times at 40 min intervals. DM 0.1, 1, and 10 $\mu g \cdot kg^{-1}$ was administered 15 min before the 2nd, 3rd and 4th coronary occlusion, respectively. The alpha$_2$-antagonist atipamezole was administered before the 5th coronary occlusion.
Measurements and Main Results: DM 1 $\mu g \cdot kg^{-1}$ significantly decreased heart rate (from 128 ± 13 to 96 ± 21 $beats \cdot min^{-1}$),10 $\mu g \cdot kg^{-1}$ DM also significantly decreased cardiac output (from 3.4 ± 1.1 to 1.4 ± 0.4 $L \cdot min^{-1}$). DM decreased myocardial blood flow in all layers of normally perfused myocardium. In hyperemic myocardium, DM significantly decreased epicardial blood flow (from 3.30 ± 1.43 to 1.44 ± 0.49 $ml \cdot min^{-1} \cdot g^{-1}$ after DM 10 $\mu g \cdot kg^{-1}$) while endocardial blood flow did not change, hereby significantly increasing the endo/epi blood flow ratio (from 0.99 ± 0.54 to 2.28 ± 0.78).
Conclusions: In the post-ischemic hyperemic subendocardial layer, coronary blood flow was preserved after DM. DM reduced primary determinants of myocardial oxygen demand. These effects of DM may be beneficial in conditions of temporary coronary artery occlusion and subsequent reperfusion.

INTRODUCTION

Dexmedetomidine (DM) is a highly specific and selective alpha$_2$-adrenoreceptor agonist.[1] Alpha$_2$ agonists are useful adjuncts to anesthesia because of their anxiolytic, sedative, sympatholytic, analgesic, anesthetic-sparing and hemodynamic-stabilizing properties.[2] Previous studies have demonstrated the ability of these drugs to decrease sympathetic and increase parasympathetic central outflow, resulting in decreased blood pressure and heart rate.[3,4] Probably due to these central effects, clonidine improved intraoperative hemodynamics, reduced intraoperative plasma catecholamines, improved myocardial ischemia and decreased post-coronary artery bypass graft hypertension.[5] On the other hand, alpha$_2$-adrenergic receptor agonists have been found to directly stimulate postjunctional receptors on vascular smooth

muscle,[16] which causes vasoconstriction. This peripheral action could oppose the centrally mediated vasodilation. Coronary vasoconstriction by stimulation of the alpha$_2$-adrenoreceptors on coronary vasculature has been demonstrated in a number of studies in dogs.[7,8] DM induced a pronounced decrease in coronary blood flow in the anesthetized dog,[9] but not in awake dogs after slow intravenous or oral administration.[10,11] During myocardial ischemia, the effects of alpha- or alpha$_2$-adrenergic stimulation are even more controversial. Heusch and co-workers reported evidence for a detrimental role of alpha$_2$-adrenergic receptor activation during sympathetic nerve stimulation and exercise in dogs with coronary stenosis.[12,13] In contrast, studies by Nathan & Feigl and Chilian & Ackell indicated that alpha-adrenergic coronary constriction exerts a favorable effect on ischemic myocardium by preventing a transmural redistribution of blood flow away from the ischemic endocardium.[14,15] In addition, Kitakaze and colleagues demonstrated that intracoronary alpha$_2$-adrenoreceptor administration may enhance the vasodilatory effects of adenosine released from the ischemic myocardium, thereby attenuating myocardial ischemia.[16]

Previous studies do not allow to predict the effect of alpha$_2$-adrenergic agonists like DM on myocardial blood flow during metabolic vasodilation. Accordingly, we studied the effects of intravenous dexmedetomidine on regional myocardial blood flow, oxygen and lactate extraction, and contractile function during reactive hyperemia following a short coronary artery occlusion in the anesthetized dog.

MATERIAL AND METHODS

General preparation

Healthy mongrel dogs of either sex and unknown age weighing 22-39 kg were studied after local animal ethical committee approval. After overnight fasting and approximately 1 hour after sedation with fentanyl 2 $\mu g \cdot kg^{-1}$ im, the dogs were anesthetized with pentobarbital sodium 30 $mg \cdot kg^{-1}$ iv. After intubation, they were ventilated with a mixture of oxygen/nitrous oxide 40/60% and halothane 1% using a Drager Pulmomat mechanical ventilator at an end-expiratory pressure of 5 cm H2O. Tidal volume (initially 15 ml/kg) and respiratory rate (12-18 per minute) were adjusted to maintain end-expired carbon dioxide concentration (Datex capnograph Oscar, Datex Instrumentation Corp., Helsinki, Finland) between 3.5 and 4.5 kPa. Oxygen saturation was monitored by pulse oximetry (Datex Oscar) and arterial blood gases were analysed every 30 min during the study. The temperature was recorded and maintained as close as possible to 37 degrees Celsius by means of a heating pad. A femoral artery was surgically exposed and a microtransducer-tipped catheter (Millar (PC 350), Houston, TX, USA) for arterial blood sampling and measurement of arterial pressure introduced into the aorta. Another microtransducer-tipped catheter was inserted via a carotid artery into the left ventricle (LV) for measurement of left ventricular cavity pressure. A thermodilution pulmonary artery catheter (Edwards VIP) was introduced

via the left internal jugular vein and floated into the pulmonary artery using the continuously displayed pressure tracing as a guide.

After administration of suxamethonium 2 mg·kg^{-1} i.v., the thorax was opened via the 5th left lateral intercostal space and the pericardium opened to expose the heart. The left anterior descending coronary artery (LAD) was prepared and an electromagnetic flow probe (Skalar, Delft, The Netherlands) placed around it near its origin. A small polyethylene catheter (PE 60, Clay Adams;1 mm in diameter and 7 cm in length) was inserted into the coronary vein — accompanying the artery — in order to obtain regional venous blood samples

Epicardial deformation

Epicardial deformation in the area that was expected to become ischemic (the perfusion area of the LAD) was measured with three inductive coils, as described in detail before.[17] These coils were attached to the epicardium in a right-angled triangle. Segment length changes in three different directions were measured. The area decrease of the epicardial region enclosed by the coils, as calculated from the length changes in the three different directions during the ejection phase, was used as an estimate of regional contractile function. Assuming that volume of a certain part of the ventricular wall is constant throughout the cardiac cycle, surface area decrease is related to wall thickening. Onset and end of the ejection phase were determined from the cross over of left ventricular pressure and ascending aortic pressure and from the dicrotic notch in the aortic pressure signal, respectively.

Hemodynamic measurements

Except for cardiac output, all hemodynamic variables measured [including heart rate, aortic pressure, LV end-diastolic pressure, LV dP/dt, LV pressure, coronary flow, mean coronary flow and ECG (lead II)] and the epicardial deformation variables were continuously displayed on an oscilloscope (Knott) and recorded on a multichannel Schwarzer recorder at 0.25 cm·sec^{-1} with the speed increased to 5 cm·sec^{-1} during data acquisition. Hemodynamic measurements were also digitized with 12 bits at 200 Hz using a DASH 16 G2 A/D convertor and stored on a Tulip Compact AT computer for further off-line analysis. Rate of change of LV pressure (dP/dt) was obtained by differentiation of the left ventricular pressure signal. The following formulae were used in order to calculate: stroke volume = cardiac output/heart rate; systemic vascular resistance = mean arterial pressure/ cardiac output and coronary vascular resistance = mean arterial pressure/myocardial blood flow. Cardiac output was measured in triplicate using cold injectate and the average taken (Edwards SAT-2 cardiac output computer).

Myocardial blood flow measurements

Radioactive microspheres (3M Company, USA) approximately 15 µm in diameter and labeled with ^{141}Ce, ^{113}Sn, ^{103}Ru or ^{95}Nb were used to determine regional myocardial

blood flow by the reference withdrawal method.[18,19] Approximately $2.5 \cdot 10^6$ microspheres were injected into the left atrium for each measurement. A reference sample was taken from the brachial artery at a rate of 20.7 $ml \cdot min^{-1}$ using a Harvard suction pump. Withdrawal of blood started 5 s before the injection of the microspheres and was continued during at least one minute. At the end of the study, the dogs were sacrificied with an overdose of pentobarbital. The heart was excised, rinsed and stored in formaldehyde 5%. Before dissection, all other chambers, great vessels, valves, and epicardial fat were removed from the left ventricle and interventricular septum. For blood flow determination, transmural samples were taken from the perfusion area of the LAD and from the posterior wall and interventricular system, perfused by the left circumflex or right coronary artery. Each sample was then divided into three layers: subendocardial, mid-wall and subepicardial. The myocardial pieces were weighed to the nearest milligram and counted in a gamma-counter (Packard Multichannel Analyzer or LKB Compugamma 1282), together with the reference blood samples. From these data myocardial blood flow in $ml \cdot min^{-1} \cdot g^{-1}$ was calculated with the MIC II program.[20]

Metabolic measurements

Blood gases and blood pH were assessed with a Radiometer ABL 3 blood gas analyser. Hemoglobin (Hb) content and oxygen saturation were determined with a Radiometer OSM-2 hemoximeter. The arterial - local coronary venous (A-CV) oxygen saturation and lactate differences were assessed. Lactate concentration was determined spectrophotometrically (Cobas Bio System, Hoffman La Roche, Basel, Switzerland). Catecholamine concentrations in plasma were determined using high-performance liquid chromatography with coulometric electrochemical detection (HPL-EC).[21] Concentrations of DM and atipamezole were determined in arterial blood (at the laboratory of Farmos, Turku, Finland).

Study protocol

Nine dogs were used in this protocol. In two dogs, multiple instrumentation failed before completion of all experiments; their metabolic data were not used for analysis. Halothane anesthesia was maintained at the same end-tidal halothane concentration of 1% throughout the entire experiment. Five min prior to the coronary occlusion, arterial and local venous blood samples were collected for measurement of blood gases, hemoglobin, oxygen saturation and plasma concentrations of lactate, DM and catecholamines. Cardiac output and all the continuously recorded hemodynamic and regional contractile variables were also determined at this timepoint. After these control measurements had been performed, the LAD was completely occluded just after the first diagonal branch during 2 minutes using a tantalium clamp. After 1 minute of occlusion, regional contractile variables were determined. After release of the occlusion, at reperfusion time 0.5 min, 1 min, 2 min, and 5 min, hemodynamic measurements were performed and blood samples were taken for determination of

oxygen saturation and lactate concentration of the local coronary venous blood; regional contractile variables were also determined at these sample times. At each sample time, registration of the hemodynamic variables was made just before blood sampling. Local venous blood was continuously withdrawn from start reperfusion to reperfusion time 0.5 min, from 0.5 to 1 min, from 1 to 2 min, and from 4 to 5 min. Microspheres were injected over a 20 sec period starting at reperfusion time 0.5 min, coinciding with peak reactive hyperemia. Fifteen minutes after release of the occlusion, measurements were repeated, followed by the administration of DM 0.1 $\mu g \cdot kg^{-1}$. Fifteen minutes after the DM administration, pre-occlusion measurements were repeated followed by another period of occlusion and reperfusion with similar measurements. This procedure was repeated another 3 times: after DM 1 and 10 $\mu g \cdot kg^{-1}$ and after the $alpha_2$-antagonist atipamezole 600 $\mu g \cdot kg^{-1}$. No microspheres were injected during the last reperfusion phase.

Statistical analysis

Data were analysed for statistical significance using the General Linear Modelling Package, SuperANOVA (Abacus Concepts, Inc., Berkeley, California) on a Macintosh Apple computer. One factor Analysis of Variance (ANOVA) and Fisher's Least Significant Difference (LSD) tests were used. $P < 0.05$ was considered significant. All results are expressed as mean ± SD.

RESULTS

Hemodynamic measurements and plasma concentrations of the catecholamines, dexmedetomidine and atipamezole

Table 1 shows the hemodynamic data and the plasma concentrations of the catecholamines, dexmedetomidine and atipamezole at control and 15 minutes following the administration of the study drugs, under normal conditions.
During peak reactive hyperemia, DM 0.1 $\mu g \cdot kg^{-1}$ decreased heart rate from 136 ± 12 to 127 ± 12 beats$\cdot min^{-1}$. DM 1 and 10 $\mu g \cdot kg^{-1}$ significantly decreased heart rate to 101 ± 16 and 82 ± 14 beats$\cdot min^{-1}$, respectively. DM 0.1 and 1 $\mu g \cdot kg^{-1}$ increased mean arterial pressure during peak reactive hyperemia from 84 ± 8 to 87 ± 9 and 85 ± 17 mmHg, respectively. DM 10 $\mu g \cdot kg^{-1}$ significantly increased mean arterial pressure to 116 ± 17 mmHg.
After atipamezole, all hemodynamic variables returned to their baseline values.
Table 1 also shows that DM 1 and 10 $\mu g \cdot kg^{-1}$ significantly decreased the plasma catecholamine concentrations.
No major arrhythmias were observed during this study and, consequently, anti-arrhythmogenic drugs or electrical defibrillation were never used.

Table 1. *The effects of dexmedetomidine and atipamezole on systemic hemodynamics and plasma concentrations of the catecholamines, dexmedetomidine and atipamezole in anesthetized dogs*

	Control	DM 0.1	DM 1	DM 10	ATI 600
Heart rate	128 ± 13	120 ± 15	96 ± 21*	81 ± 21*	118 ± 22
Mean arterial pressure	78 ± 11	79 ± 13	90 ± 12	119 ± 12*	84 ± 17
LVEDP	4.4 ± 2.6	5.8 ± 4.4	6.9 ± 4.6	11.5 ± 5.8*	4.3 ± 3.2
dP/dtmax	1647 ± 557	1350 ± 372	1347 ± 1773	1220 ± 341	1569 ± 531
Cardiac output	3.4 ± 1.1	3.0 ± 1.0	2.4 ± 0.9	1.4 ± 0.4*	3.3 ± 1.5
Stroke volume	27 ± 8	25 ± 7	25 ± 5	18 ± 6*	27 ± 9
Systemic vascular resistance	25 ± 8	28 ± 9	40 ± 11*	89 ± 26*	30 ± 13
Plasma epinephrine	1.69 ± 1.58	1.43 ± 1.01	0.29 ± 0.19*	0.3 ± 0.1*	2.36 ± 1.73
Plasma norepinephrine	0.84 ± 0.64	0.70 ± 0.45	0.12 ± 0.08*	0.43 ± 0.18*	1.41 ± 1.13
Plasma dexmedetomidine		0.04 ± 0.07	0.61 ± 0.19*	11.8 ± 6.0*	2.11 ± 0.74*
Plasma atipamezole					194 ± 73

Mean ± SD data; n = 9; * = significantly different from control value ($P < 0.05$); Abbreviations: DM = 15 minutes after the intravenous administration of dexmedetomidine in $\mu g \cdot kg^{-1}$; ATI = 15 minutes after the intravenous administration atipamezole in $\mu g \cdot kg^{-1}$; LVEDP = left ventricular end-diastolic pressure; dP/dt_{max} = first derivative of left ventricular pressure; Units: heart rate in $beats \cdot min^{-1}$; mean arterial pressure and LVEDP in mmHg; dP/dt_{max} in $mmHg \cdot s^{-1}$; cardiac output in $L \cdot min^{-1}$; stroke volume in ml; systemic vascular resistance in $mmHg \cdot min \cdot L^{-1}$; epinephrine and norepinephrine in $nmol \cdot L^{-1}$; dexmedetomidine and atipamezole in $ng \cdot ml^{-1}$.

Coronary blood flow

Figure 1 depicts the values of coronary blood flow in $ml \cdot min^{-1}$, as measured with the electromagnetic flow probe around the left anterior descending coronary artery, under normal conditions and during reactive hyperemia. Peak reactive hyperemia resulted in blood flow values approximately 3 times the baseline values. DM and atipamezole did not significantly alter blood flow under normal conditions or during peak reactive hyperemia.

Regional myocardial blood flow measurements

Figure 2 presents the data on regional myocardial blood flow in the normally perfused region and figure 3 in the hyperemic region of the left ventricular wall, as measured with radioactive microspheres injected during peak reactive hyperemia.
In the normally perfused myocardium, DM 10 $\mu g \cdot kg^{-1}$ significantly decreased blood flow in all layers: in the epicardial layer from 1.24 ± 0.74 to 0.62 ± 0.31 $ml \cdot min^{-1} \cdot g^{-1}$ and in the endocardial layer from 1.27 ± 0.66 to 0.76 ± 0.34 $ml \cdot min^{-1} \cdot g^{-1}$.
In the hyperemic region, DM 10 $\mu g \cdot kg^{-1}$ significantly decreased blood flow in the epicardial layer (from 3.30 ± 1.43 to 1.44 ± 0.49 $ml \cdot min^{-1} \cdot g^{-1}$), but in the endocardial layer blood flow did not change after DM 1 $\mu g \cdot kg^{-1}$ and even slightly increased after DM 10 $\mu g \cdot kg^{-1}$ (from 2.78 ± 1.23 to 3.21 ± 1.43 $ml \cdot min^{-1} \cdot g^{-1}$).

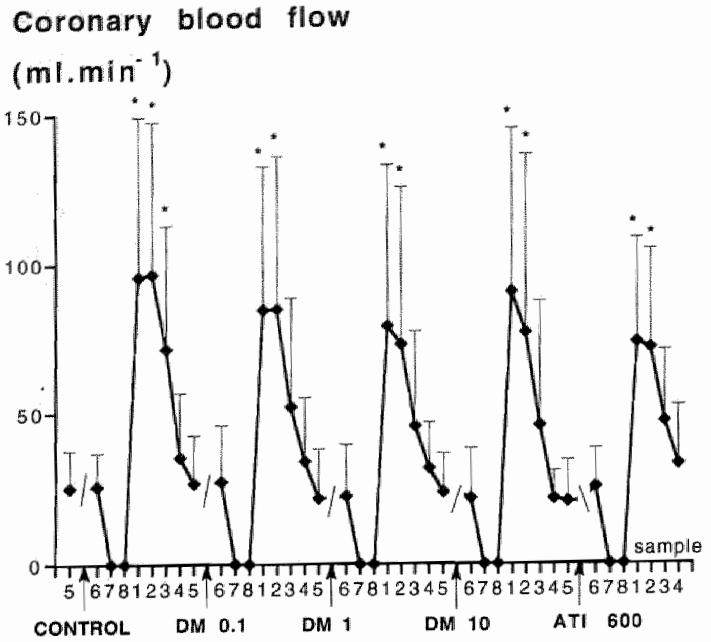

Figure 1. *The effects of dexmedetomidine and atipamezole on coronary blood flow under normal conditions and during reactive hyperemia after coronary occlusion in anesthetized dogs*
1 = after 30 sec of reperfusion; 5 = baseline flow; 2 = after 1 min of reperfusion; 6 = control flow and flow after DM and Ati; 3 = after 2 min of reperfusion; 7 & 8 = coronary occlusion; 4 = after 5 min of reperfusion; DM= dexmedetomidine; Ati= atipamezole; Mean ± SD data (n=9); * Significantly different from preceding value under normal conditions ($P<0.05$)

Figure 4 presents the endocardial/epicardial blood flow ratio. In the hyperemic region, this ratio significantly increased after DM 1 and 10 $\mu g \cdot kg^{-1}$. In the normally perfused region, only after DM, 10 $\mu g \cdot kg^{-1}$, a significant, although smaller, increase of this ratio was observed.

Table 2 shows the coronary vascular resistance in the normally perfused and hyperemic region in the epicardial-, mid-, and endocardial layer. In the normally perfused region, DM 1 $\mu g \cdot kg^{-1}$ did not alter coronary vascular resistance in any layer. After DM 10 $\mu g \cdot kg^{-1}$ coronary vascular resistance significantly increased in all myocardial layers. In the hyperemic region, while DM 1 and 10 $\mu g \cdot kg^{-1}$ significantly increased the coronary vascular resistance in the epicardial layer and midmyocardial layer, the resistance did not change in the endocardial layer.

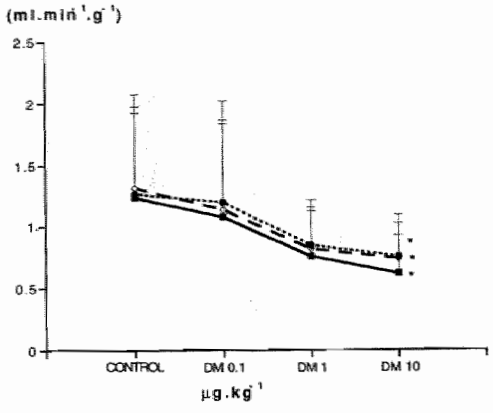

Figure 2. *The effects of dexmedetomidine on the transmural distribution of myocardial blood flow in normally perfused myocardium in anesthetized dogs*
solid line = epicardial flow; striped line = midmyocardial flow; dashed line = endocardial flow; DM = dexmedetomidine; Mean ± SD data (n=9); * Significantly different from control value (P<0.05)

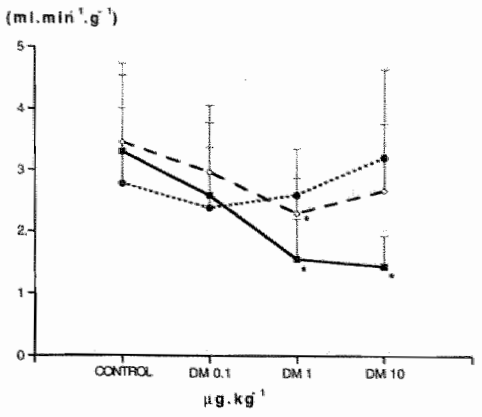

Figure 3. *The effects of dexmedetomidine on the transmural distribution of myocardial blood flow in reactive hyperemic myocardium in anesthetized dogs*
solid line = epicardial flow; striped line = midmyocardial flow; dashed line = endocardial flow; DM = dexmedetomidine; mean ± SD data (n=9); * significantly different from control value (P<0.05)

Table 2. *The effects of dexmedetomidine on the coronary vascular resistance in the different layers of the normally perfused and reactive hyperemic myocardium in anesthetized dogs*

Coronary vascular resistance	control (mmHg·min·g·ml^{-1})	DM 0.1 μg·kg^{-1}	DM 1 μg·kg^{-1}	DM 10 μg·kg^{-1}
Epicardial				
- normally perfused	90 ± 47	107 ± 50	146 ± 75	215 ± 77*
- reactive hyperemic	30 ± 13	39 ± 16	65 ± 25*	87 ± 31*
Midmyocardial				
- normally perfused	82 ± 40	93 ± 37	125 ± 49	168 ± 48*
- reactive hyperemic	26 ± 8	32 ±11	40 ± 8*	49 ± 21*
Endocardial				
-normally perfused	85 ± 45	93 ± 45	121 ± 49	166 ± 48*
- reactive hyperemic	35 ± 13	42 ± 22	36 ± 11	41 ± 18

Coronary vascular resistance = mean arterial pressure / blood flow (microspheres); DM = dexmedetomidine; Mean ± SD data; n = 9; * = significantly different from control value (P<0.05)

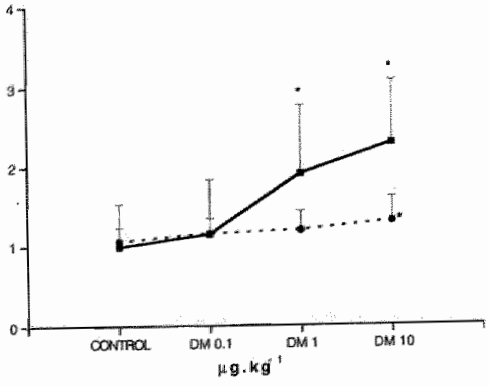

Figure 4. *The effects of dexmedetomidine on the endocardial/epicardial blood flow ratio in anesthetized dogs*
solid line = reactive hyperemic myocardium; dashed line = normally perfused myocardium; DM= dexmedetomidine; mean ± SD data (n=9); * significantly different from control value (P<0.05)

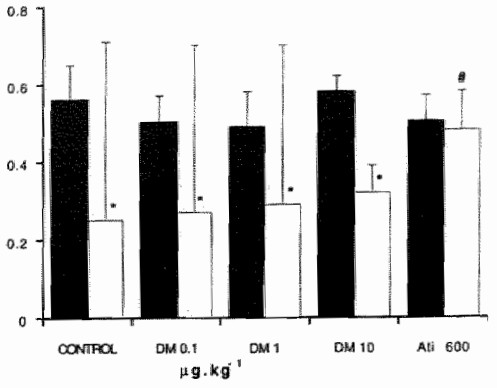

Figure 5. *The effects of dexmedetomidine and atipamezole on the (arterial-coronary venous) oxygen saturation difference before coronary occlusion (black bars) and during peak reactive hyperemia (white bars) in anesthetized dogs*
DM= dexmedetomidine; ati= atipamezole; mean ± SD data (n=7); * significantly different from preceding value under normal conditions (P<0.05); # significantly different from corresponding control value

Metabolic measurements

Figure 5 shows the arterial - coronary venous (A-CV) oxygen saturation differences pre-occlusion and during the first half minute of reperfusion. During normal perfusion, the A-CV oxygen saturation differences were not significantly influenced by increasing doses of DM. During reactive hyperemia, the A-CV oxygen saturation differences significantly decreased compared to pre-occlusion values, except for atipamezole. These values during reactive hyperemia were not influenced by the administration of DM; after atipamezole, the A-CV oxygen saturation difference during reactive hyperemia was significantly larger than during control reperfusion.

Figure 6 shows the A-CV lactate differences. During normal perfusion, the A-CV lactate difference was positive, indicating lactate uptake by the myocardium. This lactate uptake was not influenced by administration of DM or atipamezole. During reperfusion, lactate release did not change significantly with increasing doses of DM (-1.6 ± 1.3 to -0.8 ± 0.4 mmol·L^{-1} after DM 10 µg·kg^{-1}). Following atipamezole, lactate release (-2.1 ± 0.4 mmol·L^{-1}), on the average, exceeded baseline values and was significantly larger than during the reperfusion phases after DM 0.1,1 and 10 µg·kg^{-1}.

Regional contractile function measurements

Figure 7 presents the effects of DM and atipamezole on epicardial surface area decrease. Under normal conditions, DM 10 µg·kg^{-1} significantly reduced surface area

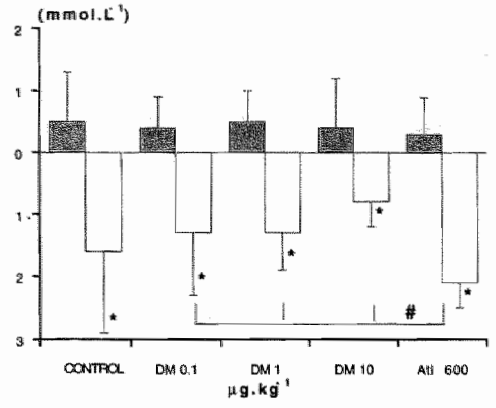

Figure 6. *The effects of dexmedetomidine and atipamezole on the (arterial-coronary venous) lactate difference before coronary occlusion (shaded bars) and during peak reactive hyperemia (white bars) in anesthetized dogs*
DM= dexmedetomidine; Ati= atipamezole; Mean ± SD data (n=7); * significantly different from preceding value under normal conditions (P<0.05); # significantly different from lactate releases after DM 0.1,1 and 10 µg·kg-1 (P<0.05)

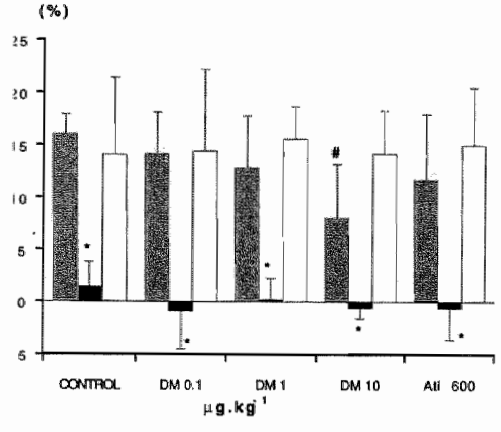

Figure 7. *The effects of dexmedetomidine and atipamezole on epicardial surface area decrease before (shaded bars) and during (black bars) coronary occlusion and during peak reactive hyperemia (white bars) in anesthetized dogs*
DM= dexmedetomidine; Ati= atipamezole; Mean ± SD data (n=9); * significantly different from preceding value under normal conditions (P<0.05); # significantly different from corres-ponding time-point at control state (P<0.05)

decrease as compared to control. During coronary stenosis, surface area decreases were severely disturbed and not significantly different from zero. DM and atipamezole had no effect on the reduction of surface area decrease during the stenoses. During reperfusion, DM and atipamezole had no effect on the recovery of regional contractile function.

DISCUSSION

The present study describes the effects of DM on blood flow in normally perfused and hyperemic myocardium. Under normal conditions, DM 1 and 10 µg·kg^{-1} decreased coronary blood flow in all myocardial layers. The calculated coronary vascular resistance increased after DM, indicating vasoconstriction. However, the unchanged

oxygen and lactate extraction indicate adequate adaptation of myocardial blood flow to metabolic requirements. This behaviour has also been reported when heart rate was varied by atrial pacing.[22] In contrast, after a noradrenaline infusion oxygen extraction was found to increase.[23] Findings from the present study indicate that systemic DM in the doses administered does not interfere with local coronary flow regulation in normal coronary arteries of the anesthetized dog.

DM reduced primary determinants of oxygen demand, such as heart rate. Our data indicate that the reduction in coronary blood flow in the myocardium under normal conditions is probably primarily due to metabolic vasoregulation rather than to adrenergic vasoconstriction.

This is the first report describing the transmural distribution of myocardial blood flow following DM during reactive hyperemia. In the hyperemic epicardial layer, DM decreased blood flow to a similar extent as in the normally perfused epicardial layer, but in the more vulnerable[24,25] hyperemic endocardial layer blood flow did not change. DM had no effect on the recovery of metabolic and functional parameters after the occlusions.

Our results are in contrast with findings that alpha$_2$-adrenergic activation by exercise or nerve stimulation can induce myocardial ischemia.[12,13] Our data neither substantiate the findings of Hori and co-workers. These authors described a beneficial effect of alpha$_2$-adrenoreceptor stimulation in experimental myocardial ischemia: enhancement of the vasodilatory effect of adenosine released from ischemic myocardium and augmentation of the hyperemic response of coronary blood flow to adenosine.[26,27] We cannot fully substantiate Hori's hypothesis as we found no decrease in coronary vascular resistance during reactive hyperemia after DM. However, the decrease of myocardial oxygen demand after DM in our experiment presumably resulted in a smaller build-up of adenosine during the occlusion periods. Subsequently, one would expect the reactive hyperemic flow to decrease after DM. The unchanged reactive hyperemic flow in the endocardium therefore could indicate that DM potentiates adenosine released from the ischemic myocardium.

In the present study, changes in the distribution of blood flow during reactive hyperemia following DM indicate preservation of blood flow in the more vulnerable endocardial layer. This finding is similar to that reported by Nathan & Feigl and Chilian & Ackell in the ischemic myocardium following adrenergic stimulation.[14,15] Our results are also in agreeement with the findings of Johannsen and coworkers who found that sympathetic nerve stimulation produced primarily subepicardial vasoconstriction in dogs with adenosine-induced maximal coronary vasodilation, even when heart rate and perfusion pressure were constant,[28] showing that hemodynamic changes are not the only factors responsible for the redistribution of blood flow.

There are several possible explanations for this beneficial preservation of endocardial blood flow during reactive hyperemia. Reactive hyperemia has been attributed to the effect of the vasodilator nucleoside adenosine,[29] which accumulates during the period of obstructed coronary blood flow. However, as metabolic vasodilation is more pronounced in the endocardial layer as compared to the epicardial layer,[30] it is possible that this vasodilation can overrule adrenergic vasoconstriction in the endo-

cardial layer but not in the epicardial layer. There is also evidence that hypoxia and acidosis can impair adrenergic coronary vasoconstriction.[31-33] As the degree of ischemia is most severe in the subendocardial layer during hypoperfusion with a greater build-up of ischemic metabolites or hypoxia, this may also explain the absence of vasoconstriction in the endocardial layer. A buildup of ischemic metabolites could also impair adrenergic neurotransmission via presynaptic mechanisms and limit endocardial adrenergic constriction. Other possibilities for non-uniform transmural coronary constriction could be related to a gradient in the density of coronary alpha-adrenergic receptors across the left ventricular wall, or in the density of the sympathetic nerves. However, these possibilities are not supported by findings in the literature.[28,34]

Experimental model considerations

In the present study, serial coronary artery occlusions were used to test the effect of DM on metabolically vasodilated myocardium. In this way, each animal served as its own control. The set-up was such that short (2 min) occlusions were followed by long (40 min) periods of recovery. This experimental design did not result in myocardial stunning or metabolic impairment: before each occlusion, there was complete recovery of regional contractile function and oxygen and lactate uptake. The recovery of the hemodynamic parameters and regional blood flow to baseline values after the $alpha_2$ antagonist atipamezole also demonstrates the stability of the experimental preparation.

It is not likely that ischemic preconditioning[35] was effective in the present experiment, because 40 min reperfusion periods were allowed after each occlusion and it has been shown that the protective action of preconditioning is transient and wanes quite rapidly following reperfusion.[36,37]

Following the 2 min coronary artery occlusions, the peak of reactive hyperemia occurred between 30 and 60 seconds after release of the occlusion. Using rapid (2 sec) microsphere injection, Downey and co-workers showed that after occlusions lasting 90 seconds, the peak of reactive hyperemia occurred earlier in the epicardial than in the endocardial layer.[38] Because we were interested in time-averaged blood flow in metabolically dilated vaculature, the microspheres were injected relatively slow (over 20 sec), thus largely excluding that a possible effect of DM on the time course of reactive hyperemia in each of the myocardial layers would interfere with the measured distribution of blood flow. The results presented in figure 1 indicate that DM had no significant influence on the time course of reactive hyperemia.

Extrapolation to man

To our knowledge, there is only one report until now describing the effects of $alpha_2$-adrenergic stimulation on the coronary vasculature in man.[39] Indolfi and co-workers found that the intracoronary administration of an $alpha_2$ agonist produced a reduction in coronary blood flow in humans with angiographically normal coronary

arteries,whereas in patients with coronary artery stenosis regional coronary blood flow decreased after alpha$_2$-receptor blockade. Indolfi's findings in humans seem compatible with our observations in dogs: while alpha$_2$ agonists increased coronary vascular resistance by 28% in humans with normal coronary arteries and more than 50% in dogs, no increase in coronary vascular resistance was found in patients with coronary stenosis or in dogs during reperfusion. This suggests that alpha$_2$-adrenergic agonists do not produce untoward coronary vasoconstriction in ischemic myocardium and may explain the positive experience with these drugs in patients with congestive heart failure,[40] as well as in patients with coronary artery disease.[5,41-43]

The overall cardiovascular effect of alpha$_2$ agonists is determined by the relative preponderance of central versus peripheral effects. This overall effect in humans is a centrally mediated lowering of the blood pressure with a decrease in heart rate, but peripheral effects may dominate the central effects when the dose of these drugs is very high, initially following a rapidly given intravenous bolus and when the pre-existing tone is low and not much room is available for the central sympatholytic effects of these drugs to manifest themselves.[10,11,44] There is evidence to suggest that in dog the peripheral vasoconstrictive effects of alpha adrenergic stimulation is more predominant as compared to humans.[11,45-47]

Conclusions

In the post-ischemic hyperemic subendocardial layer, coronary blood flow was preserved after dexmedetomidine.
Dexmedetomidine reduced primary determinants of myocardial oxygen demand. These effects of DM may be beneficial in conditions of temporary coronary artery occlusion and subsequent reperfusion.
More extensive investigations in humans are needed before the exact role of dexmedetomidine as an anesthetic adjuvant in patients with ischemic heart disease can be determined.

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CHAPTER 7

Beneficial effects of dexmedetomidine on ischaemic myocardium of anaesthetized dogs

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Beneficial effects of dexmedetomidine on ischaemic myocardium of anaesthetized dogs

ABSTRACT

We have studied the effect of dexmedetomidine during coronary artery stenosis (CAS) in dogs. Three periods of 15 min of CAS were induced at 40-min intervals in 2 groups of dogs (dexmedetomidine compared with placebo). Dexmedetomidine was administered before the second and third periods of CAS in doses of 1 and 3 $\mu g \cdot kg^{-1}$, repectively.

Dexmedetomidine decreased plasma concentrations of noradrenaline by 71 ± 9%, heart rate by 8 ± 4%, cardiac output by 30 ± 6%, and increased mean arterial pressure by 23 ± 10%. Dexmedetomidine reduced blood flow in non-ischaemic myocardium and in the ischaemic epicardial layer by 16 ± 8%, but blood flow was preserved in the ischaemic midmyocardial and subendocardial layers. Consequently, dexmedetomidine increased the ischaemic/non-ischaemic blood flow ratio. Dexmedetomidine did not change myocardial oxygen consumption but decreased myocardial oxygen demand from 4.91 ± 0.33 to 3.76 ± 0.25 $\mu mol \cdot min^{-1} \cdot g^{-1}$, thereby reducing the oxygen deficiency of the ischaemic myocardium from 1.47 ± 0.37 to 0.29 ± 0.32 $\mu mol \cdot min^{-1} \cdot g^{-1}$.

Key words: Sympathetic nervous system, adrenergic agonists. Heart, myocardial function. Sympathetic nervous system, dexmedetomidine. Heart, ischaemia. Heart, blood flow, myocardial. Dog.

INTRODUCTION

Preliminary studies suggest that the perioperative use of dexmedetomidine may result in a decreased risk of adverse cardiac events, including myocardial ischaemia.[1] This probably depends on a centrally mediated sympatholytic effect which decreases catecholamine-mediated stress responses. In contrast with these beneficial central effects, alpha$_2$ agonists may also cause peripheral and coronary vasoconstriction by stimulation of postjunctional alpha$_2$-adrenergic receptors. The effect of this vasoconstriction during myocardial ischaemia is controversial. Heusch and Deussen presented evidence that alpha$_2$-adrenoreceptor activation can worsen ischaemia.[2] In contrast, other investigators reported that alpha-adrenoreceptor stimulation can beneficially modulate coronary blood flow during myocardial ischaemia by preventing transmural redistribution of blood flow away from ischaemic endocardium.[3]

The aim of this study was to determine if systemic dexmedetomidine has beneficial effects on ischaemic myocardium in an animal model known to be highly sensitive to the direct, peripheral vasoconstrictor effect of alpha$_2$ agonists.

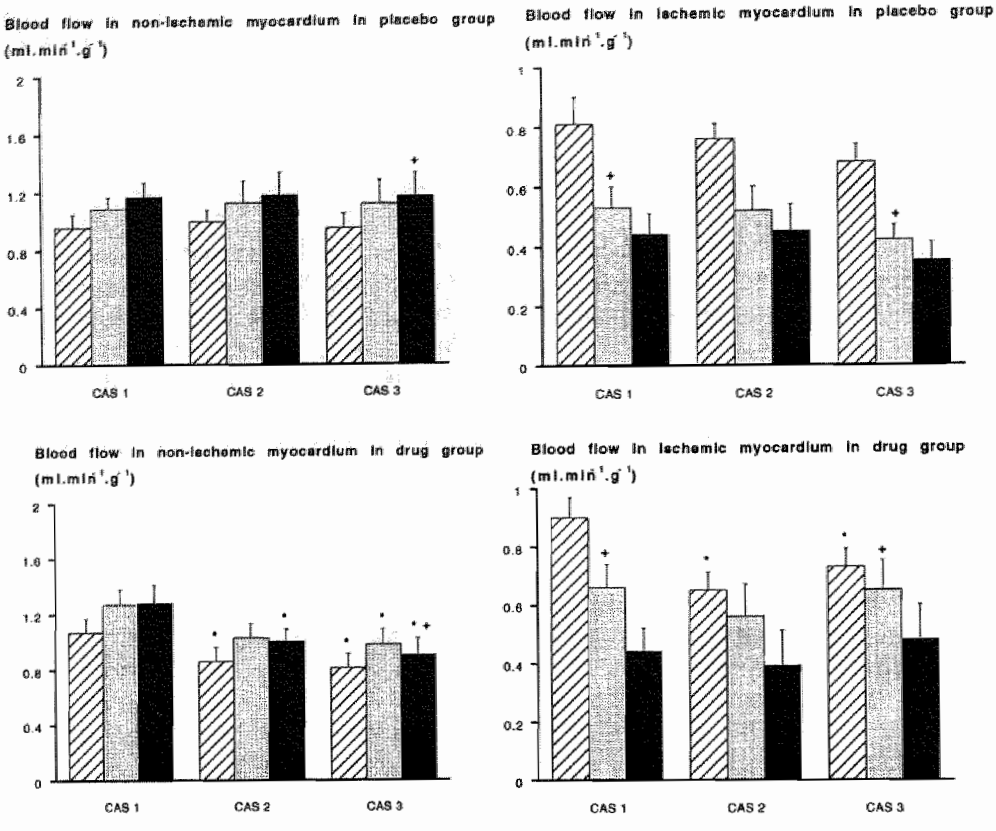
METHODS AND RESULTS

After obtaining animal Ethics Committee approval, mongrel dogs were anaesthetized with pentobarbital and their lungs ventilated with 1% halothane and nitrous oxide in oxygen. The dogs were instrumented, as described previously,[4] to measure aortic and left ventricular pressure and cardiac output. A cuff was placed on the left descending coronary artery (LAD). Coronary pressure was measured distal to the cuff. The degree of stenosis was controlled by keeping constant mean perfusion pressure distal to the stenosis using a Servo system feeding a motor-pump, which determined the degree of cuff inflation. Global myocardial oxygen demand was estimated using the pressure-work index.[5] Regional oxygen consumption was measured from blood flow (radioactive microspheres) and local arterial-coronary venous oxygen content difference. Oxygen deficiency was calculated by substracting oxygen consumption from oxygen demand.

Five minutes before the first period of CAS, control blood samples were obtained and haemodynamic measurements were performed. Thereafter, CAS 1 was induced by reducing mean pressure in the LAD distal to the stenosis to 40% of mean arterial pressure. After 12 minutes of stenosis, microspheres were injected. Two minutes later, blood samples were obtained and haemodynamic measurements performed. Thereafter, the CAS was released. Twenty minutes after release of the stenosis, measurements were repeated, followed by administration of dexmedetomidine 1 $\mu g \cdot kg^{-1}$ in the active drug group (n=11) and saline in the placebo group (n=9). Twenty minutes after administration of dexmedetomidine, measurements were repeated followed by a second period of stenosis. Measurements during stenosis and the subsequent recovery period were the same as during the first episode of stenosis. This procedure was repeated a third time after administration of dexmedetomidine 3 $\mu g \cdot kg^{-1}$ in the drug group.

A two-way ANOVA for repeated measures was used for inter-group comparisons. Intragroup comparisons were evaluated using one-way ANOVA for repeated measures and Fisher's Protected LSD test as post-hoc test. Baseline values between the two groups were compared using Student's t test. $P < 0.05$ was considered significant. Results are expressed as mean ± SEM.

Dexmedetomidine decreased heart rate (from 126 ± 6 to 114 ± 5 beats$\cdot min^{-1}$), dP/dt_{max} (from 1371 ± 128 to 1177 ± 62 mmHg$\cdot s^{-1}$) and cardiac output (from 4.2 ± 0.3 to 2.4 ± 0.4 L$\cdot min^{-1}$) and increased mean arterial pressure (from 81 ± 4 to 98 ± 4 mmHg) and systemic vascular resistance (from 1572 ± 131 to 3902 ± 563 dyne$\cdot s \cdot cm^{-5}$). In the placebo group, no haemodynamic changes were observed throughout the study.



Regional blood flow distribution in non-ischaemic (left) and ischaemic (right) myocardium in the placebo group (upper) and in the drug group (lower) as measured with radioactive microspheres.
Transmural samples were taken from the perfusion area of the LAD (ischaemic myocardium) and from the posterior wall and interventricular septum (non-ischaemic myocardium). Samples were divided into subendocardial, mid-wall and subepicardial layers. In this way, coronary blood flow could be measured simultaneously in non-ischaemic and ischaemic myocardium during the three stenoses. Striped bars = epicardial flow; grey bars = midmyocardial flow; black bars = endocardial flow; CAS = coronary artery stenosis; mean ± SEM data; n = 9 in placebo group; n = 11 in drug group; * = significantly different from corresponding CAS 1 value; + = significantly different from corresponding value in other group

Dexmedetomidine decreased plasma concentrations of norepinephrine from 121 ± 17 to 25 ± 12 pg·ml^{-1}.
After dexmedetomidine 3 µg·kg^{-1}, ischaemic/non-ischaemic blood flow ratios were significantly higher in the epicardial (from 0.81 ± 0.07 to 0.93 ± 0.09) and endocardial layers (from 0.33 ± 0.06 to 0.47 ± 0.10) compared to placebo (fig. 1).
Dexmedetomidine increased haemoglobin concentration from 7.2 ± 0.2 to 8.4 ± 0.3 mmol·L^{-1} and decreased myocardial oxygen demand from 4.91 ± 0.33 to 3.76 ± 0.25 µmol·min^{-1}·g^{-1}. Regional myocardial oxygen consumption did not change after

dexmedetomidine (from 3.08 ± 0.39 to 3.20 ± 0.51 $\mu mol \cdot min^{-1} \cdot g^{-1}$). Dexmedetomidine decreased myocardial oxygen deficiency from 1.47 ± 0.37 to 0.29 ± 0.32 $\mu mol \cdot min^{-1} \cdot g^{-1}$.

DISCUSSION

In this study, dexmedetomidine decreased myocardial oxygen demand and reduced blood flow in non-ischaemic myocardium. This was related to its haemodynamic effects: reduction in heart rate and dP/dt_{max}. Blood flow in the ischaemic inner layers was preserved. In this way, the ischaemic/non-ischaemic blood flow ratio decreased and myocardial oxygen deficiency was reduced.

The effects of dexmedetomidine on regional blood flow in ischaemic myocardium are in accordance with studies on the effects of aspecific alpha-blockade or stimulation during ischaemia.[3] Preservation of blood flow in ischaemic myocardium by $alpha_2$ agonists is probably caused by the more powerful local metabolic stimuli during ischaemia, which overrule adrenergic vasoconstriction. As the degree of ischaemia is most severe in the inner layers during hypoperfusion, adrenergic vasoconstriction in this region is inhibited to a greater extent than in the outer layer.
Distal to a flow limiting stenosis, such specific epicardial vasoconstrictive effect may lead to improvement of endocardial perfusion, the "reverse steal" effect.[3]
The decrease in heart rate after dexmedetomidine could be an additional explanation for this beneficial effect on blood flow, because slowing of the heart rate favours endocardial relative to epicardial perfusion. The different findings of Heusch and Deussen[2], who found that $alpha_2$-adrenergic activation can worsen myocardial ischaemia, may be explained by differences in preparation, degree of ischaemia, anaesthesia and intensity and mode of alpha-adrenergic stimulation.

Our preparation was expected to be highly sensitive to the direct, peripheral vasoconstrictor effect of dexmedetomidine.[4] Compared with humans, we therefore may have overestimated the coronary vasoconstrictive effects and underestimated the central sympatholytic effects of dexmedetomidine. This could also underestimate a possible anti-ischaemic effect of dexmedetomidine, because it was shown that systemic clonidine had anti-ischaemic properties, while intracoronary administration caused vasoconstriction.[6] However, these results should be extrapolated with caution to potential clinical use in humans as the results relate only to halothane-anesthetized dogs. Halothane not only has marked haemodynamic effects, but could also have influenced the sympathetic responses.

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CHAPTER 8

The effects of alpha$_2$-adrenergic stimulation with mivazerol on myocardial blood flow and function during coronary artery stenosis in anesthetized dogs

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The effects of alpha$_2$-adrenergic stimulation with mivazerol on myocardial blood flow and function during coronary artery stenosis in anesthetized dogs

ABSTRACT

The central sympatholytic effect of alpha$_2$ agonists may be beneficial during myocardial ischemia, but could be opposed by their peripheral vasoconstrictive effect. We studied the effects of mivazerol during periods of moderate coronary artery stenosis in anesthetized dogs. Mivazerol decreased heart rate (from 125 ± 6 to 106 ± 6 beats·min^{-1}) and cardiac output (from 4.4 ± 0.6 to 1.8 ± 0.2 L·min^{-1}) under normal conditions, while mean arterial pressure did not change. Mivazerol reduced blood flow in nonischemic myocardium and in the ischemic epicardial layer, but blood flow was preserved in the ischemic midmyocardial and subendocardial layer. Mivazerol had no effect on myocardial oxygen extraction during the stenoses, and regional myocardial oxygen consumption was unchanged. However, mivazerol decreased myocardial oxygen demand from 4.51 ± 0.51 to 3.17 ± 0.24 μmol·min^{-1}·g^{-1}, thereby reducing oxygen deficiency of ischemic myocardium to values significantly lower than in the placebo group (from 1.07 ± 0.32 to 0.47 ± 0.41 μmol·min^{-1}·g^{-1}). Mivazerol had no effect on myocardial lactate production during the stenoses. We conclude that mivazerol reduced myocardial oxygen demand while blood flow was preserved in the inner layers of ischemic myocardium.

Key words: alpha$_2$-adrenergic agonists, cardiac function, mivazerol, myocardial ischemia, regional myocardial blood flow

INTRODUCTION

Alpha$_2$-adrenergic receptor agonists are useful adjuncts to anesthesia because of their anxiolytic, sedative, analgesic, anesthetic-sparing, sympatholytic, and hemodynamic stabilizing properties.[1] There is evidence that the central effects of alpha$_2$ agonists may be beneficial in patients with ischemic heart disease.[2]

On the other hand, alpha$_2$ agonists can also cause peripheral and coronary vasoconstriction by stimulation of postjunctional alpha$_2$-adrenergic receptors.[3] The effect of peripheral alpha-adrenergic vasoconstriction during experimental myocardial ischemia is controversial. Heusch et al[4,5] reported evidence for a detrimental role of alpha$_2$-adrenoreceptor activation during sympathetic nerve stimulation and exer-

cise in dogs with coronary stenosis. In contrast, other reports indicated that nonspecific alpha-adrenergic coronary constriction exerts a favorable effect on ischemic myocardium by preventing a transmural redistribution of blood flow away from the subendocardial layer.[6,7]

Mivazerol is a new, highly specific and selective alpha$_2$-adrenoreceptor agonist (UCB SA Pharma Sector, Braine l'Alleud, Belgium).[8] Preliminary reports suggest that mivazerol has anti-ischemic effects both in animals and in humans.[9,10]

The aim of the present study was to investigate whether mivazerol can protect the ischemic myocardium in an animal model known to be highly sensitive to the direct, peripheral vasoconstrictor effect of alpha$_2$ agonists. Therefore, the effects of mivazerol on regional myocardial blood flow, metabolic variables and regional contractile function were assessed during moderate coronary artery stenosis (CAS) in the anesthetized dog.

MATERIAL AND METHODS

General preparation

Mongrel dogs (23-38 kg) were studied after local animal ethical committee approval. After premedication with fentanyl 2 $\mu g \cdot kg^{-1}$ intramuscularly, the dogs were anesthetized with pentobarbital 30 $mg \cdot kg^{-1}$ intravenously and ventilated with oxygen/nitrous oxide 40/60% and halothane 1%. Microtransducer-tipped catheters (Millar (PC 350), Houston, TX) were introduced into the aorta and into the left ventricle. A pulmonary artery catheter was introduced via an internal jugular vein. After suxamethonium 2 $mg \cdot kg^{-1}$ intravenously, the thorax was opened via the fifth left lateral intercostal space. An electromagnetic flow probe and an inflatable cuff were placed circumferentially distal to the first diagonal branch of the left descending coronary artery (LAD). Coronary artery pressure was measured via a catheter, inserted in the coronary artery distal to the cuff. The degree of stenosis was controlled by keeping constant the mean perfusion pressure distal to the site of the stenosis using a servosystem feeding a motor pump, which determined the degree of inflation of the cuff around the LAD.[11] Another catheter was inserted into the coronary vein accompanying the artery to obtain regional venous blood samples.

Epicardial deformation

Epicardial deformation in the perfusion area of the LAD was measured with three inductive coils, as previously described.[12] These coils were attached to the epicardium in a right-angled triangle. Segment length changes in three different directions were measured. The area decrease of the epicardial region enclosed by the coils, as calculated from the length changes in the three different directions during the ejection phase, was used as an estimate of regional contractile function. Assum-

ing that volume of a certain part of the ventricular wall is constant throughout the cardiac cycle, surface area decrease is related to wall thickening.

Hemodynamic measurements

All the continuously measured parameters were displayed on an oscilloscope (Knott) and recorded on a multichannel Schwarzer recorder at 0.25 cm·sec^{-1} with the speed increased to 5 cm·sec^{-1} during data acquisition. Hemodynamic measurements were also digitized with 12 bits at 200 Hz using a DASH 16 G2 A/D convertor and stored on a Tulip Compact AT computer for further off-line analysis. Coronary vascular resistance was calculated as the quotient of distal LAD pressure and myocardial blood flow. The percentage coronary artery stenosis was calculated as [(mean arterial pressure -coronary artery pressure)/ mean arterial pressure] ·100%. Myocardial oxygen demand was estimated using the Pressure Work Index.[13] Regional oxygen consumption was calculated using the data of blood flow and oxygen extraction. Oxygen deficiency was calculated by substracting oxygen consumption from oxygen demand. Cardiac output was measured in triplicate using cold injectate and the average taken (Edwards SAT-2 cardiac output computer).

Myocardial blood flow measurements

Radioactive microspheres, approximately 15 µm in diameter, were used to determine regional myocardial blood flow, as previously described.[11] Approximately 2.5·10^6 microspheres were injected into the left atrium for each measurement. A reference sample was taken from the brachial artery at a rate of 20.7 ml·min^{-1} using a Harvard infusion/withdrawal pump. After the dogs were killed, transmural samples were taken from the perfusion area of the LAD (ischemic myocardium) and from the posterior wall and interventricular system (nonischemic myocardium). Samples were divided into subendocardial, midwall and subepicardial layers. In this way, coronary blood flow could be measured simultaneously in non-ischemic and ischemic myocardium during the three stenoses. All samples were weighed and counted in a gamma-counter. From these data blood flow in ml.min^{-1}·g^{-1} was calculated with the MIC II program.

Metabolic measurements

Blood gas tensions and blood pH were assessed with a Radiometer ABL 3 blood gas analyser. Hemoglobin (Hb) content and oxygen saturation were determined with a Radiometer OSM-2 hemoximeter. Lactate concentration was determined spectrophotometrically (Cobas Bio System, Hoffman La Roche, Basel, Switzerland). Catecholamine concentrations in plasma were determined using high-performance liquid chromatography with coulometric electrochemical detection. Concentrations of mivazerol were determined at the Laboratory of Drug Metabolism and Pharmacokinetics of UCB SA Pharma Sector, Braine l' Alleud, Belgium.

Study protocol

Twenty-one acutely instrumented dogs, in which three sequential CAS were applied, were studied. Decreases in cardiac output and dP/dt_{max} during the first stenosis were used as an estimate of the area at risk. To obtain a study group with a similar area at risk, five dogs were excluded from the study because changes in cardiac output and dP/dt_{max} during the first stenosis were minimal or very large. In this way, 16 dogs with similar hemodynamic changes during the first stenosis could be studied. In 8 dogs (drug group), mivazerol in two different doses was administered before the second and third CAS, while in the placebo group (n=8) coronary stenoses were applied in a similar manner without drug administration. Reperfusion periods of 40 min were allowed after each ischemic episode. Halothane anesthesia was maintained at 1% throughout the experiment.

Five minutes prior to each CAS, control blood samples were taken, cardiac output was measured and all the continuously recorded hemodynamic variables were determined. Subsequently, mean pressure distal to the stenosis was decreased to about 40% of mean systemic arterial pressure. After 12 min of stenosis, microspheres were injected. After 14 min of stenosis, blood samples were taken and hemodynamic measurements were performed. Thereafter, the CAS was gradually released over a 3-min period. Recovery of coronary artery flow was checked using the traces of the flowprobe.

Twenty minutes after release of the first stenosis, recovery measurements of the hemodynamic and metabolic parameters were performed. Thereafter, mivazerol was administered in the drug group aiming at a target plasma concentration of 1 $ng \cdot ml^{-1}$, using pharmacokinetic variables from beagle dogs. To this purpose, an initial infusion of mivazerol 50 $\mu g \cdot kg^{-1} \cdot h^{-1}$ was given over 5 min and a maintenance infusion of mivazerol started at the rate of 0.8 $\mu g \cdot kg^{-1} \cdot h^{-1}$ using infusion pumps. Twenty minutes after the start of the mivazerol infusion, control measurements were repeated followed by the second stenosis. After the second recovery measurements, the dose of mivazerol was increased in the drug group aiming at a target plasma concentration of 2 $ng \cdot ml^{-1}$ by using an initial dose of mivazerol of 35 $\mu g \cdot kg^{-1} \cdot h^{-1}$ over 5 min and by increasing the maintenance infusion of mivazerol to 1.1 $\mu g \cdot kg^{-1} \cdot h^{-1}$.

Statistical analysis

A two-way analysis of variance for repeated measures was used for intergroup comparisons. Intragroup comparisons were evaluated using one-way analysis of variance for repeated measures and Fisher's protected least significant difference test as *post-hoc* test. Baseline values between the two groups were compared using Student's *t*-test. $P < 0.05$ was considered significant. All results are expressed as mean ± SEM.

Table 1. *Hemodynamic measurements and plasma concentrations of the catecholamines in the placebo group of anesthetized dogs*

		CAS 1	CAS 2	CAS 3
Heart rate (beats·min^{-1})	control	123 ± 6	115 ± 6	108 ± 6
	stenosis	116 ± 8	123 ± 7^{+}	121 ± 9^{+}
Mean arterial pressure (mmHg)	control	86 ± 3	87 ± 6	80 ± 4
	stenosis	88 ± 5	86 ± 6	89 ± 8
Left ventricular end-diastolic pressure (mmHg)	control	9 ± 1	11 ± 1	9 ± 1
	stenosis	10 ± 1	12 ± 2	11 ± 2
dP/dt_{max} (first derivative of LV pressure) (mmHg·s^{-1})	control	1513 ± 66	1383 ± 73	1362 ± 94^{+}
	stenosis	1397 ± 61	1439 ± 73^{+}	1384 ± 104^{+}
Cardiac output (L·min^{-1})	control	4.1 ± 0.4	3.5 ± 0.3^{+}	3.8 ± 0.4^{+}
	stenosis	3.4 ± 0.3$^{\#}$	3.9 ± 0.5^{+}	3.4 ± 0.4^{+}
Systemic vascular resistance (dyne·s·cm^{-5})	control	1750 ± 116	2120 ± 294^{+}	1781 ± 179^{+}
	stenosis	2159 ± 219	2007 ± 331^{+}	2250 ± 281^{+}
Distal coronary pressure (mmHg)	control	82 ± 5	80 ± 5^{+}	73 ± 3*
	stenosis	34 ± 2$^{\#}$	32 ± 2$^{\#}$	32 ± 3$^{\#}$
Percent coronary stenosis	stenosis	61 ± 2	63 ± 1	64 ± 2
Myocardial oxygen demand (μmol·min^{-1}·g^{-1})	control	4.48 ± 0.35	4.01 ± 0.29	3.94 ± 0.33^{+}
	stenosis	4.11 ± 0.34	4.37 ± 0.42^{+}	4.14 ± 0.40^{+}
Myocardial oxygen consumption (μmol·min^{-1}·g^{-1})	stenosis	2.66 ± 0.27	2.88 ± 0.58	2.62 ± 0.36
Hemoglobin in arterial blood (mmol·L^{-1})	control	7.3 ± 0.3	7.5 ± 0.2^{+}	7.4 ± 0.3^{+}
Arterial-coronary venous oxygen saturation (%)	control	0.58 ± 0.06	0.60 ± 0.06	0.53 ± 0.09
	stenosis	0.65 ± 0.05	0.71 ± 0.06	0.51 ± 0.15
Arterial-coronary venous oxygen content (mmol·L-1)	control	3.93 ± 0.25	4.22 ± 0.32	4.28 ± 0.37
	stenosis	4.68 ± 0.35$^{\#}$	5.25 ± 0.24$^{\#}$	4.98 ± 0.45
Norepinephrine (pg·ml^{-1})	control	121 ± 36		
	stenosis	107 ± 21	108 ± 35	166 ± 45^{+}
Epinephrine (pg·ml^{-1})	control	164 ± 59		
	stenosis	221 ± 79	145 ± 57	220 ± 66
Mivazerol (ng·ml^{-1})	control	0 ± 0	0 ± 0^{+}	0 ± 0^{+}

Mean ± SEM data; n=8; CAS = coronary artery stenosis; LV= left ventricular; control= 5 min before CAS; stenosis = after12-14 min of CAS; * = significantly different from corresponding CAS 1 value; # = significantly different from preceding control value; + = significantly different from corresponding value in the drug group.

RESULTS

Hemodynamic measurements and plasma concentrations of the catecholamines and mivazerol.

In the placebo group (Table 1), control values (before each CAS) of these variables were not significantly different from each other, apart from the distal coronary pressure before CAS 3.
In the drug group (Table 2), mivazerol dose-dependently decreased heart rate, dP/dt_{max} and cardiac output and increased left ventricular end-diastolic pressure and systemic vascular resistance.
In both groups, cardiac output significantly decreased during the first stenosis compared to the pre-stenosis control values.
In the drug group, dP/dt_{max} was significantly lower during than before the first stenosis, but not significantly different from the corresponding value in the placebo group.
The norepinephrine plasma concentration was significantly lower in the drug group compared to the placebo group after the higher dose of mivazerol.
In the placebo group, oxygen extraction significantly increased during CAS 1 and CAS 2 compared to pre-stenosis control values.
Mivazerol significantly increased oxygen extraction in the absence of CAS, but did not influence oxygen extraction during CAS. No significant differences were found between the two study groups.

Myocardial blood flow

In nonischemic and ischemic myocardium of the placebo group, no significant changes in subepicardial, midmyocardial or subendocardial blood flow were observed between the three periods of CAS (Figure 1).

Mivazerol decreased blood flow in all three layers of the non-ischemic myocardium. In contrast, in the ischemic myocardium of the drug group, blood flow decreased only in the epicardial layer. The difference between the 2 groups was only significant for the ischemic subepicardial layer during CAS 3.

Coronary vascular resistance

In the placebo group, no significant changes were observed in the coronary vascular resistance (Figure 2).

Mivazerol increased coronary vascular resistance in all layers of the nonischemic myocardium. In the ischemic myocardium, mivazerol increased only coronary vascular resistance in the subepicardial layer. No significant differences were found in the ischemic myocardium between the two groups.

Table 2. *Hemodynamic measurements and plasma concentrations of the catecholamines and mivazerol in the drug group of anesthetized dogs*

		CAS 1	CAS 2	CAS 3
Heart rate (beats·min^{-1})	control	125 ± 6	109 ± 5	106 ± 6*
	stenosis	126 ± 3	106 ± 3*+	99 ± 4*+
Mean arterial pressure (mmHg)	control	87 ± 8	98 ± 9	91 ± 5
	stenosis	85 ± 7	94 ± 4	90 ± 5
Left ventricular end-diastolic pressure (mmHg)	control	8 ± 1	14 ± 1*	12 ± 2*
	stenosis	7 ± 1	12 ± 2*	13 ± 2*
dP/dt_{max} (first derivative of LV pressure) (mmHg·s^{-1})	control	1551 ± 131	1280 ± 115*	1134 ± 61*+
	stenosis	1412 ± 91#	1208 ± 85*+	1049 ± 65*+
Cardiac output (L·min^{-1})	control	4.4 ± 0.6	2.5 ± 0.3*+	1.8 ± 0.2*+
	stenosis	3.8 ± 0.5#	2.3 ± 0.3*+	1.7 ± 0.2*+
Systemic vascular resistance (dyne·s·cm^{-5})	control	1560 ± 176	3972 ± 1086*+	4311 ± 541*+
	stenosis	1851 ± 283	4158 ± 1052*+	4741 ± 914*+
Distal coronary pressure (mmHg)	control	75 ± 3	96 ± 9*+	86 ± 5*
	stenosis	34 ± 2#	39 ± 2#	38 ± 2#
Percent coronary stenosis	stenosis	59 ± 3	58 ± 1	58 ± 2
Myocardial oxygen demand (µmol·min^{-1}·g^{-1})	control	4.51 ± 0.51	3.82 ± 0.42*	3.17 ± 0.24*+
	stenosis	4.05 ± 0.30	3.45 ± 0.24*+	2.97 ± 0.23*+
Myocardial oxygen consumption (µmol·min^{-1}·g^{-1})	stenosis	2.83 ± 0.13	2.87 ± 0.21	2.50 ± 0.41
Hemoglobin in arterial blood (mmol·L^{-1})	control	7.1 ± 0.2	8.7 ± 0.5*+	8.7 ± 0.4*+
Arterial-coronary venous oxygen saturation (%)	control	0.51 ± 0.03	0.57 ± 0.03	0.58 ± 0.02
	stenosis	0.68 ± 0.02#	0.62 ± 0.03	0.62 ± 0.05
Arterial-coronary venous oxygen content (mmol·L^{-1})	control	3.66 ± 0.22	5.11 ± 0.18*	5.04 ± 0.33*
	stenosis	4.81 ± 0.18#	5.35 ± 0.25	5.15 ± 0.44
Norepinephrine (pg·ml^{-1})	control	82 ± 12		
	stenosis	89 ± 13	57 ± 18	51 ± 14+
Epinephrine (pg·ml^{-1})	control	257 ± 95		
	stenosis	191 ± 58	385 ± 304	257 ± 190
Mivazerol (ng·ml^{-1})	control	0 ± 0	1.39 ± 0.29*+	1.82 ± 0.13*+~

Mean ± SEM data; n=8; CAS = coronary artery stenosis; LV = left ventricular control = 5 min before CAS; stenosis = after 12-14 min of CAS; * = significantly different from corresponding CAS 1 value; # = significantly different from preceding control value; + = significantly different from corresponding value in the placebo group; ~ = significantly different from corresponding CAS 2 value.

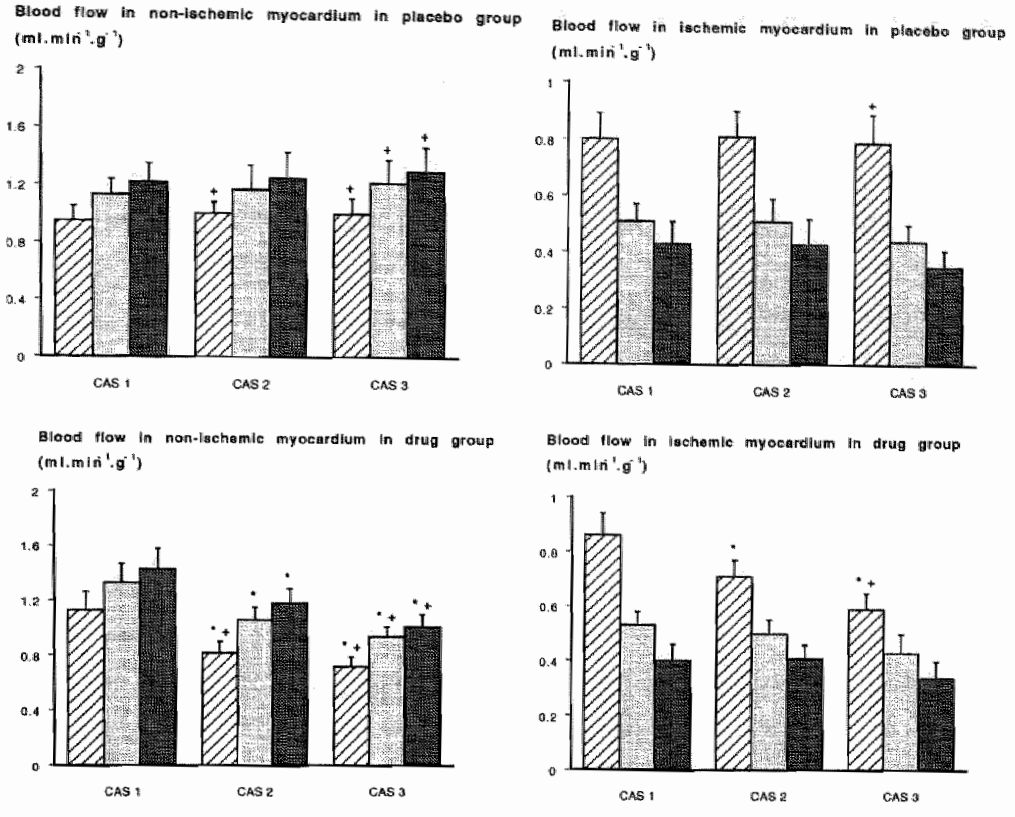

Figure 1. *Regional blood flow distribution in non-ischemic (left) and ischemic (right) myocardium in the placebo group (upper) and in the drug group (lower)*
Striped bars = epicardial flow; light grey bars = midmyocardial flow; dark grey bars = endocardial flow; *CAS = coronary artery stenosis*; Mean ± SEM data; n = 8 in both groups; * = Significantly different from corresponding CAS 1 value ; + = Significantly different from corresponding value in other group (Note the doubling of the flow scale in the non-ischemic myocardium as compared to the ischemic myocardium).

Myocardial metabolism and regional contractile function

All three consecutive episodes of CAS decreased the arterial-cronary venous lactate difference in both groups to the same extent. No significant differences were found between the two study groups (Figure 3).

In the placebo group, no significant differences were observed between the three control and recovery values of surface area decrease (Figure 3). Stenosis reduced surface area decrease to a similar extent during the three stenoses.

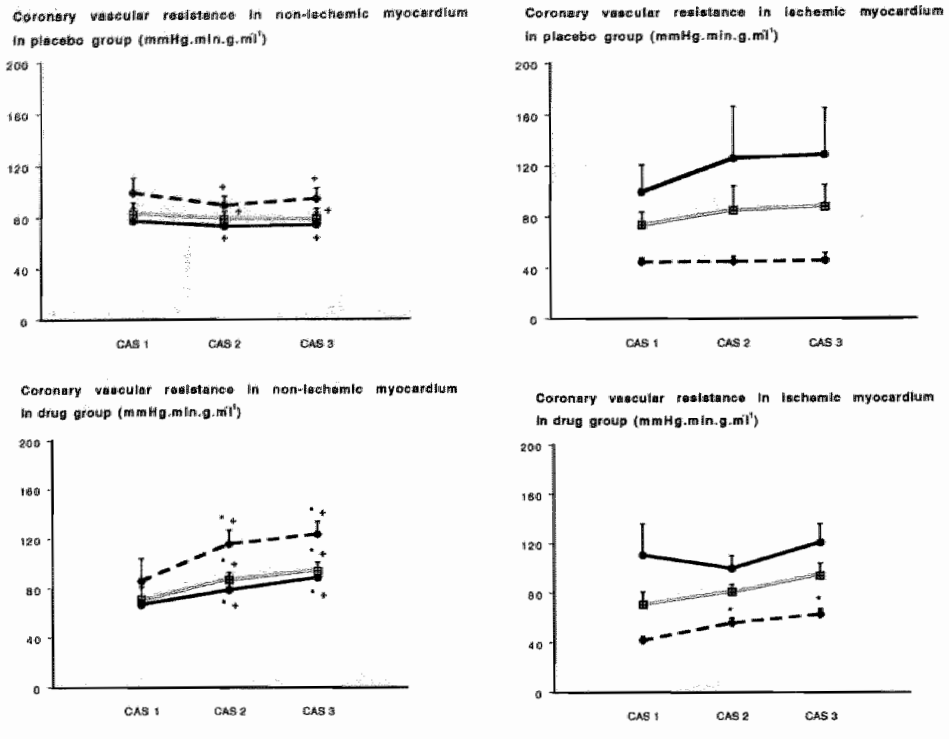

Figure 2. *Coronary vascular resistance in non-ischemic (left) and ischemic (right) myocardium in the placebo group (upper) and in the drug group (lower)*
Striped line = epicardial flow; grey line = midmyocardial flow; solid line = endocardial flow; CAS = coronary artery stenosis; Mean ± SEM; n = 8 in both groups; * = significantly different from corresponding CAS 1 value; + = significantly different from corresponding value in other group.

In the drug group, mivazerol dose-dependently reduced surface area decrease before onset of the stenoses. Surface area decrease during the third stenosis was significantly lower than during the first stenosis.

No significant differences were found between the two study groups.

Myocardial oxygen deficiency

As shown in Figure 4, myocardial oxygen deficiency during the second and third CAS was significantly lower in the mivazerol group than in the placebo group.

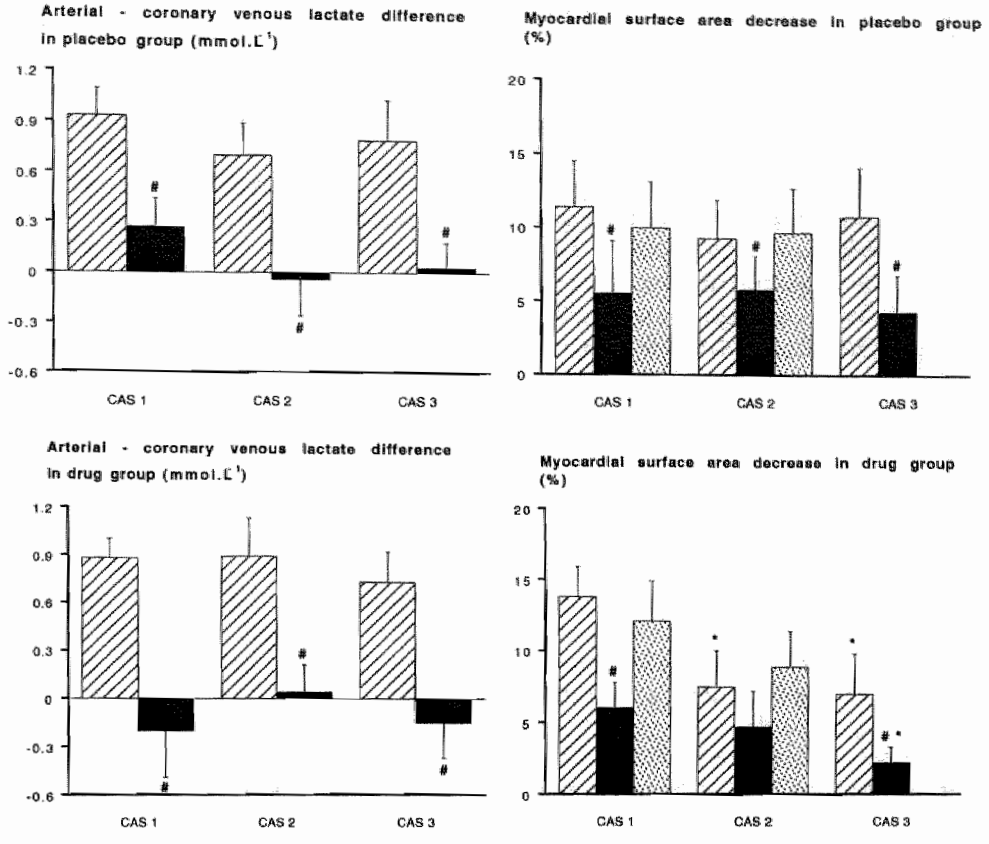

Figure 3. *Arterial - coronary venous lactate differences (left) and myocardial surface area decreases in the placebo group (upper) and in the drug group (lower)*
Striped bars = before coronary stenosis; dark grey bars = during stenosis; light grey bars = 10 min after release of stenosis; CAS = coronary artery stenosis; Mean ± SEM data; n = 8 in both groups; * = significantly different from corresponding CAS 1 value; # = significantly different from preceding control value.

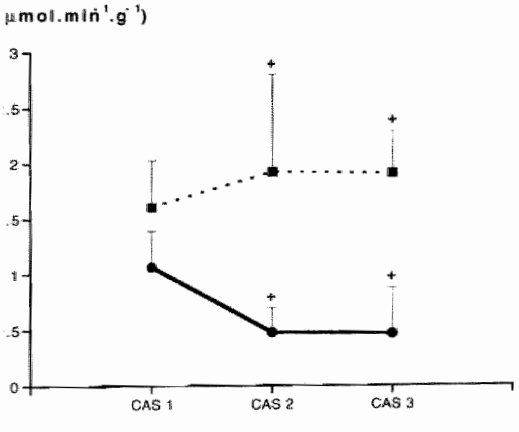

Figure 4. *Myocardial oxygen deficiency in the placebo group and in the drug group*
Striped line = placebo group; solid line = drug group; CAS = coronary artery stenosis; mean ± SEM data; n = 8 in both groups; + = significantly different from corresponding value in other group.

DISCUSSION

The hemodynamic effects of mivazerol (increases in systemic vascular resistance and left ventricular end-diastolic pressure and reductions in heart rate, cardiac output, and dP/dt_{max}) are similar to those of other alpha$_2$ agonists, both in animal and in humans.[14,15]

In the present study, mivazerol reduced myocardial oxygen demand and blood flow in non-ischemic myocardium. However, blood flow and oxygen consumption of ischemic myocardium did not decrease, thereby reducing oxygen deficiency of the ischemic myocardium to values significantly lower than in the placebo group. These changes did not result in altered metabolism or contractile function of ischemic myocardium.

Mivazerol decreased myocardial oxygen demand due to its hemodynamic effects and increased arterial hemoglobin content. These effects decrease myocardial perfusion requirements. Other investigators have shown that alpha-adrenergic vasoconstriction can compete with this metabolic vasoregulation.[16] In the present experiment, although there was a significant increase in oxygen extraction after mivazerol, no change in lactate production was observed. This suggests that the reduction of coronary blood flow in non-ischemic myocardium was probably primarily due to metabolic vasoregulation rather than to adrenergic vasoconstriction.

There are several possible explanations for the beneficial preservation of blood flow in the ischemic endocardial layer by mivazerol. Mivazerol decreased heart rate and slowing of heart rate is known to favor endocardial relative to epicardial perfusion since endocardial flow occurs mainly in diastole.[17] Also, metabolic vasodilation could overrule adrenergic vasoconstriction in these layers. This possibility is supported by evidence that hypoxia and acidosis can impair adrenergic coronary vasoconstriction.[17] As the degree of ischemia is most severe in the inner layers during hypoperfusion,[17] inhibition of adrenergic vasoconstriction may be larger in these layers. Other possibilities for non-uniform coronary vasoconstriction, like a gradient in the density of coronary alpha-adrenergic receptors or sympathetic nerves, are not supported by other experimental findings.[18]

Our results are in contrast with findings that alpha$_2$-adrenergic actvation by exercise or nerve stimulation can induce myocardial ischemia.[4,5] The different findings may be explained by differences in the preparation, degree of ischemia, anesthesia and intensity and mode of alpha-adrenergic stimulation. Our results also do not substantiate the findings of Kitakaze and co-workers[19] who reported a vasodilatory effect of intracoronary clonidine in ischemic myocardium of beta-blocked anesthetized dogs. In our experiments, mivazerol did not decrease vascular resistance in the ischemic myocardium.

Regional contractile function decreased with increasing doses of mivazerol, probably related to the decreased overall myocardial contractility. Therefore, the decreased regional contractile function during the third stenosis as compared to the first stenosis appears to be primarily related to this decreased contractility rather than to aggravated ischemia. This idea is supported by the finding that changes in surface

area decrease from control to stenosis were not significantly different between CAS 1 and CAS 3.

Canine versus human alpha$_2$-adrenergic stimulation

Our preparation was expected to be highly sensitive to the direct, peripheral vasoconstrictor effect of mivazerol. Firstly, sympathetic outflow was low in these anesthetized, unstressed animals. This would limit the central sympatholytic effect of the drug and emphasize the peripheral effect. Secondly, Bloor et al[15] suggested that the peripheral vasoconstrictive effects of alpha adrenergic stimulation are more pronounced in dogs than in humans.[15] The dose-response relationship, however, is so steep that only a full exploration of different doses would clarify that postulate. Nevertheless, administration of dexmedetomidine 2 $\mu g \cdot kg^{-1}$ in humans resulted in a 100% increase in systemic vascular resistance[15] and a 28% increase in coronary vascular resistance.[20] In contrast, we found a 160% increase in systemic vascular resistance and a 50% increase in coronary vascular resistance in anesthetized dogs. Similarly, Schmeling et al[21] reported a 180% increase in systemic vascular resistance in awake dogs after dexmedetomidine 1.25 $\mu g \cdot kg^{-1}$. We may have overestimated the coronary vasoconstrictive effects and uderestimated the central sympatholytic effects of mivazerol compared to humans. This could also underestimate a possible anti-ischemic effect of mivazerol, because Heusch et al[22] showed that the central effects of systemic clonidine had anti-ischemic properties, while the intracoronary administration caused coronary vasoconstriction.

There is only one report describing the effects of alpha$_2$-adrenergic stimulation on the coronary vasculature in humans.[20] Intracoronary administration of an alpha$_2$ agonist produced a reduction in coronary blood flow in humans with angiographically normal coronary arteries. In patients with CAS, regional coronary blood flow decreased after alpha$_2$-receptor blockade, probably related to prejunctional release of norepinephrine. This suggests that alpha$_2$-adrenergic agonists do not produce untoward coronary vasoconstriction in ischemic myocardium.

Experimental model considerations

In the present study, an experimental model of three repetitive moderate coronary artery stenoses of short duration followed by myocardial reperfusion periods was used, allowing to use each dog as its own control.

We used distal coronary artery pressure rather than percent reduction of flow or percent narrowing of coronary artery to control the degree of stenosis. One of the advantages of this method is that during coronary stenosis distal pressure can still be measured accurately. Moreover, in ischemic myocardium, autoregulation is almost exhausted and coronary blood flow highly depends on perfusion pressure. Another advantage of this technique is that the post-stenotic coronary artery pressure takes into account the pressure transmitted through the stenosis and through the collaterals, which may be considerable in the dog.[23] In validation studies of this method, it

was shown that within and between individuals reproducible stenoses could be induced.[24] Using this technique, if arterial blood pressure would be different between the various episodes of CAS, this would also affect coronary perfusion pressure. The same would be the case if a fixed stenosis was applied. In this study, the pharmacological intervention did not lead to significant differences in perfusion pressure during any of the stenoses. Moreover, by calculation of the coronary vascular resistance, influences of perfusion pressure on residual blood flow were taken into account.

It is not likely that ischemic preconditioning was effective in our experiment, because 40-minute reperfusion periods were allowed after each ischemic episode and the protective action of preconditioning is transient and wanes quite rapidly following reperfusion.[25] The moderate degree of ischemia also did not induce myocardial stunning. This is evidenced by the recovery of surface area decrease after each stenosis in the placebo group. Also, no hemodynamic changes were seen under nonischemic conditions prior to the second and third period of CAS, indicating the stability of the model. Hemodynamic changes caused by the first CAS in the placebo group were not significantly different from hemodynamic changes caused by the first CAS in the drug group (prior to the drug administration). We therefore assumed that the area at risk was similar in both groups.

Conclusions

We conclude that mivazerol decreased myocardial oxygen demand and reduced blood flow in non-ischemic myocardium. Because mivazerol did not change blood flow in underperfused midmyocardial and subendocardial layers, oxygen deficiency of ischemic myocardium was less than in the placebo group. These effects were not accompanied by changes in metabolism and function of ischemic myocardium.

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CHAPTER 9

The effect of mivazerol on perioperative hemodynamic stability and myocardial ischemia

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Perioperative sympatholysis: effects of an alpha-2 adrenoreceptor agonist, mivazerol on hemodynamic stability, myocardial ischemia, and adverse events
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The effect of mivazerol on perioperative hemodynamic stability and myocardial ischemia

ABSTRACT

Background: In vitro and animal studies have demonstrated anti-ischemic properties of mivazerol related to sympathetic modulation. To evaluate the safety and efficacy of mivazerol in patients subjected to profound stress, a multicenter phase II clinical trial was performed to assess effects on hemodynamic stability and myocardial ischemia in patients at risk for coronary artery disease undergoing vascular surgery.
Methods: Following institutional approval, 300 patients from 23 European Medical Centers participated in this study. The allocated patient cohort for the Maastricht Center was 14 patients. Patients received either high-dose mivazerol (HDM: 1.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$, n=98), low dose mivazerol (LDM: 0.75 $\mu g \cdot kg^{-1} \cdot h^{-1}$, n=99), or placebo (PL, n=103), for 72 hours continuously, commencing prior to anesthesia, continuing throughout surgery, and ending on the third postoperative day.
Results: Compared with placebo, HDM significantly decreased the incidence of tachycardia during the intraoperative (HDM = 30%, LDM = 38%, PL = 51%; P = 0.002), early (0-24 hrs) postoperative (HDM = 29%, LDM = 51%, PL = 50%; P = 0.002), and late (24-72 hrs) postoperative (HDM = 46%, LDM = 54%, PL = 70%; P = 0.001) periods. The incidence of hypertension was significantly decreased during the intraoperative period (HDM = 46%, LDM = 43%, PL = 63%,; P = 0.021). There was no difference in treatment for bradycardia or in the incidence of hypotension between the groups.
Intraoperative myocardial ischemia was significantly lower in the high-dose group (HDM = 20%, LDM = 23%, PL = 34%; P = 0.026, HDM vs PL). When the intraoperative period was divided was divided into non-emergence and emergence period, the incidence of myocardial ischemia was significantly decreased in the high-dose group during emergence (HDM = 11%, LDM = 19%, PL = 30%; P = 0.003).
Conclusions: Mivazerol decreased the incidence of tachycardia, hypertension, and measures of myocardial ischemia, particularly during high stress periods.

INTRODUCTION

The stress during and after surgery is associated with increased sympathetic activity which may be manifested as hemodynamic instability. Tachycardia and hypertension may result in increased myocardial oxygen demand and reduced supply (at higher heart rates). In the presence of a compromized circulation, the imbalance between supply and demand could lead to myocardial ischemia and, possibly, serious adverse outcome.[1,2]

Alpha$_2$-adrenoreceptor agonists have centrally-mediated sympatholytic, sedative, analgesic and anxiolytic effects, thereby enabling stabilization of the sympathetic nervous system and attenuation of catecholamine response to perioperative stress. Thus, alpha$_2$ agonists may prevent the occurence of perioperative hyperdynamic changes, mitigating imbalances in myocardial oxygen supply-demand, and possibly the incidence of myocardial ischemia.[3,4]

The new alpha$_2$-adrenoreceptor agonist mivazerol was shown to blunt the surge of plasma catecholamines induced by surgical stress, to decrease the basal norepinephrine concentrations and appears to demonstrate anti-ischemic properties in animal models of myocardial ischemia.[5-7] In clinical pharmacology studies, mivazerol produced a decrease in basal plasma norepinephrine levels, an early and transient increase in afterload, mild bradycardia, and negative inotropic effects at higher doses. In patients with stable angina undergoing a treadmill exercise tolerance test, mivazerol exhibited anti-ischemic and anti-anginal activity.[8]

The aim of the present study was to investigate whether mivazerol could afford hemodynamic stability in patients at high risk for coronary artery disease undergoing vascular surgery and general anesthesia. Mivazerol's effect on the incidence and severity of perioperative myocardial ischemia and adverse clinical outcome was also determined.

METHODS

Following institutional approval and informed consent, three hundred patients from 23 European medical centers participated in this placebo-controlled, double-blind, randomized, parallel-group trial. Eligible study patients were those scheduled for vascular surgery (excluding aortic surgery) under general anesthesia lasting for at least one hour. The patient group was comprised of patients with coronary artery disease or in the population group at risk for coronary artery disease.

Coronary artery disease was confirmed by one or more of the following: 1) history of typical angina pectoris or atypical angina with an ischemic response to exercise or scintigraphic evidence of myocardial perfusion defect; 2) history of myocardial infarction; 3) Q wave on ECG typical of infarction without a history; 4) coronary artery disease by angiography; 5) two or more of the following risk factors: age 65 years, current smoking, plasma cholesterol 240 mg/dl, treated diabetes, and treated hypertension. Patients received either high-dose mivazerol (HDM: 1.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$, n=98), low dose mivazerol (LDM: 0.75 $\mu g \cdot kg^{-1} \cdot h^{-1}$, n=99), or placebo (PL, n=103), for 72 hours continuously, commencing prior to anesthesia, continuing throughout surgery, and ending on the third postoperative day (POD). The perioperative anesthetic management was standardized and systolic blood pressure and heart rate were prescribed to be maintained within 20% of preoperative baseline values by using prespecified anesthetic changes and cardiovascular drugs. Prophylactic use of ischemia therapy was specifically prohibited. Hemodynamics (blood pressure and heart rate) were monitored continuously for 96 hours, and myocardial ischemia was

assessed using Holter electrocardiography for at least 8 hours prior to induction of anesthesia and continuing until 96 hours postoperatively. Twelve-lead electrocardiograms (ECG) and creatine phosphokinase isoenzymes (CK-MB) were obtained preoperatively and over multiple prespecified periods postoperatively.

Hemodynamic episodes were defined for the intraoperative period as: HR > 20% increase from baseline or HR < 40 bpm, and SBP > 20% increase or SBP < 20% decrease from baseline, with episodes lasting for at least 5 min; for the postoperative period, episodes were defined as: HR < 40 or HR > 100 bpm, and SBP < 90 or SBP > 180 mmHg. In addition, cardiovascular treatment for correction of hemodynamic changes (tachycardia, bradycardia, hypertension, hypotension) were recorded and characterized.

An *electrocardiographic ischemic episode* was defined as a reversible ST segment change, lasting at least one minute, and involving a shift from baseline of either: 0.1 mV ST segment depression at J + 40 msec, or 0.2 mV ST segment elevation at the J point. The baseline ST segment was defined as the average ST segment over a period of 15-60 minutes preceding each episode. Reversibility was defined as a return to baseline of the ST segment for at least one minute. Each episode was assessed for duration, magnitude, severity (area-under-the-curve/AUC) as well as for ischemic burden (minute of ischemia/hours monitored).

Myocardial infarction was diagnosed if any of three criteria were met: 1) new Q wave on a postoperative 12-lead ECG using Minnesota Code quantitation (1-1 to 1-3) and investigator panel validation, or 2) CK-MB elevation-either elevation of CK-MB concentration to 100 $ng \cdot ml^{-1}$ at any time post surgery or elevation of CK-MB concentration to 70 $ng \cdot ml^{-1}$ at any time after 12 hours post surgery, or 3) acute MI diagnosed via autopsy.

The primary measures of efficacy were hemodynamic instability (tachycardia, hypertension) and the use of cardiovascular medications to treat instability. The secondary measures were myocardial ischemia (incidence and severity) and the use of ischemia medications. Safety was assessed via adverse clinical events, hemodynamic abnormalities (bradycardia, hypotension), and the use of cardiovascular medications to treat hemodynamic abnormalities.

Data and Statistical Analysis

All research data (Holter ECG, hemodynamic, 12-lead ECG data) were analysed at the coordinating center (IREF, San Francisco, CA, USA) in a blinded fashion to ensure that uniform data analysis criteria were employed. Block randomization was performed within each of the 23 centers; thus, the analyses presented here include an adjustment for center effect.

For the analysis of the incidence of hemodynamic or ischemic episodes, when the outcome variable was binary and the explanatory variable was treatment, the two-by-three contingency table analysis was controlled for center effect using the Cochran-Maentel-Hanszel general association Chi-square statistic. For the high-dose versus placebo comparison, the same technique was performed using data for

the high-dose and placebo groups. These analyses were performed using PROC FREQ of the Statistical Analysis System (SAS, SAS Institute, Cary, SC). For a continuousresponse variable, a general linear model was used and included center and treatment-by-center effects in order to derive the adjusted treatment effect.

The treatment-by-center effect was included in all models, regardless of whether the efffect was statistically significant or not (at the 5% level), because the sample size per center was not sufficiently large to assess adequately whether there was treatment-by-center effect, and because randomization was carried out within each center. Furthermore, in most of the models, the center effect was significant, suggesting a high level of heterogeneity in the least-square estimated means of the response variable across the 23 centers. PROC GLM (General Linear Model) was used to fit these models and to obtain the adjusted estimated treatment efffect. The comparison between high-dose and placebo was carried out using data from the high-dose and placebo groups, and the same technique as described was used.

The secondary efficacy variables included myocardial ischemia, anesthetic and analgesic requirements, and adverse clinical outcomes. For these endpoints, incidence was compared using either Chi-square or Fisher's Exact Test. ANOVA or Kruskal-Wallis methods were used to analyze characteristics of hemodynamic and ischemic abnormalities. For analysis of area-under-the-CK-MB-curve and the maximum CK-MB, the data window was taken to be four hours post surgery to 96 hours post surgery, which encompassed fourteen measurements of CK-MB. Area-under-the-CK-MB-curves and maximum CK-MB values were compared across treatment groups using ANOVA techniques. Missing data were considered unevaluable; therefore, they were not included in the analysis. However, since the values were missing at random across study groups, the statistical inferences were still generalizable for the whole sample size.

RESULTS

Compared with placebo, high-dose mivazerol significantly decreased the incidence of tachycardia during the intraoperative, early postoperative (0-24 hrs) and late postoperative (24-72 hrs) periods. The number of patients receiving treatment for tachycardia was significantly less in the high-dose mivazerol group (vs placebo) during the early and late postoperative period.

		Intraoperative	Early postop	Late postop
Tachycardia	HDM	30%	29%	46%
	LDM	38%	51%	54%
	PL	51%	50%	70%
	P	0.002	0.002	0.001
Treatment for tachycardia	HDM		10%	6%
	LDM		20%	13%
	PL		20%	15%
	P		0.043	0.024

The incidence of hypertension was significantly decreased during the intraoperative period (HDM = 46%, LDM = 43%, PL = 63%; P = 0.021), and treatment for hypertension exhibited a trend (HDM = 33%, LDM = 34%, PL = 46%; P = 0.062, HDM vs PL).

The incidence of bradycardia was increased in the low-dose and high-dose mivazerol groups during drug administration (intraoperative, early and late postoperative period) and after drug discontinuation. However, there was no difference in treatment for bradycardia during and after drug administration.

		Intraoperative	Early postop	Late postop	Drug disconti
Bradycardia	HDM	9%	6%	6%	6%
	LDM	7%	5%	4%	6%
	PL	3%	0%	0%	0%
	P	0.091	0.043	0.659	0.088
Treatment for bradycardia	HDM	32%	4%	1%	2%
	LDM	32%	3%	2%	0%
	PL	36%	1%	4%	1%
	P	0.978	0.395	0.422	0.322

The incidence of hypotension was similar between the three groups during the monitoring periods, and there was no difference in the treatment for hypotension.

Intraoperative myocardial ischemia was significantly lower in the high-dose group (HDM = 20%, LDM = 23%, PL = 34%; P = 0.026, HDM vs PL). When the intraoperative period was divided into non-emergence and emergence period, the incidence of myocardial ischemia was significantly decreased in the high-dose group during emergence (HDM = 11%, LDM = 19%, PL = 30%; P = 0.003).

Adverse cardiac outcomes occurred in 3% of HDM, 2% of LDM, and 8% of PL patients, and myocardial infarction was diagnosed in 2% of HDM patients, 1% of LDM patients and 6% of PL patients (P = 0.118).

Conclusions

Mivazerol, when administered to high-risk patients for 72 hours continuously perioperatively, appears to be safe, without significant hypotension or adverse events, but with evidence of bradycardia which was not associated with clinical adverse events. Regarding efficacy, mivazerol appears to mitigate the incidence of, and treatment for, tachycardia, hypertension, and measures of myocardial ischemia, particularly during high-stress periods. Thus, these salutary effects of mivazerol on efficacy surrogates indicate further study in large-scale trials assessing mivazerol' effect on adverse cardiac outcome.

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CHAPTER 10

Summary and conclusions

Alpha$_2$-adrenergic receptors are widely distributed in various animal and human tissues. These receptors mediate a variety of physiological functions, depending on the adrenoceptor type and the tissue. Therefore, the activation of adrenoceptors represent the net effect of sometimes conflicting actions at different sites.

Alpha$_2$-adrenergic receptor agonists are drugs that activate these receptors. In 1964, the prototypical alpha$_2$ agonist clonidine was tested for possible use as a nasal decongestant. Volunteers receiving intranasal clonidine became very sleepy and their heart rate and blood pressure decreased. It was decided therefore by the pharmaceutical company to further study clonidine for it's anti-hypertensive properties. In 1966, clonidine was introduced into clinical practice for the treatment of hypertension. The sedative and antisialic effects of clonidine certainly must have limited the popularity of the drug when used as chronic anti-hypertensive medication.

In recent years, interest has been focused on the application of clonidine in the perioperative period. In addition to decreased sympathoadrenal activity to provide more cardiovascular stability, clonidine has been shown to cause sedation, anxiolysis, analgesia, decreased salivation and to reduce anesthetic requirements. These effects of clonidine might be especially beneficial in patients with severe systemic diseases. Data from preliminary studies in small patient groups suggest that clonidine may decrease the incidence of myocardial ischemia in high-risk cardiovascular patients.

In this thesis, we studied whether the new, specific and selective alpha$_2$-adrenoreceptor agonists like dexmedetomidine and mivazerol could be beneficial anesthetic adjuvants in the perioperative period in patients at risk for coronary artery disease. To this purpose, a series of laboratory investigations was designed to study potential anti-ischemic mechanisms of action of dexmedetomidine and mivazerol. Special attention was paid to their central sympatholytic effect, their systemic cardiovascular effects, and to their effects on perfusion and function of normal and ischemic myocardium. In addition, we studied - together with investigators from The Multicenter Study of Perioperative Ischemia Group (McSPI) from other European Medical Centers -the effect of mivazerol on perioperative hemodynamic stability and myocardial ischemia in 300 patients at risk for coronary artery disease.

Dexmedetomidine and mivazerol consistently caused profound sympatholysis with decreases in circulating catecholamines. The clinical dose of 1 μg·kg-1 dexmedetomidine decreased heart rate by 20%, increased mean arterial pressure by 25% and decreased cardiac output by 32% (*chapters 4, 6 and 7*). Mivazerol decreased heart rate by 13%, increased mean arterial pressure by 13% and decreased cardiac output by 43% (*chapter 8*). In 8 dogs we measured left ventricular pressure-volume relations with the conductance catheter technique, before and after the administration of 1

$\mu g \cdot kg^{-1}$ dexmedetomidine. dP/dt_{max}, which is a pre-and afterload dependent index of contractility, decreased approximately 10-20%, but not always significantly. End-systolic elastance and preload-recruitable stroke work, pre- and afterload independent variables of contractility, decreased 45% and 40%, respectively. Left ventricular ejection fraction decreased 35%. *(R. Frietman, J.J. Schreuder, F.W. Prinzen, P.M.H.J. Roekaerts and S. de Lange: Pressure-volume relationships in the left ventricle during use of dexmedetomidine. Ned Tijdschr Geneeskd 139 (30): 1575, 1995).* Thus, alpha$_2$ agonists significantly decrease cardiac contractility. However, it is most important to note that long and extensive clinical experience with clonidine has not produced any evidence of adverse effects on cardiac and coronary function. On the contrary, clonidine has been used successfully in patients with coronary artery disease, as well as in patients with congestive heart failure. It is becoming increasingly apparent that the optimum way of anesthetizing patients with ischemic heart disease is to "reduce the determinants of myocardial oxygen demand". *(WK Hamilton: Do let the blood pressure drop and do use myocardial depressants! Anesthesiology 45(3): 273-274, 1976).*

The reductions in heart rate and contractility after dexmedetomidine and mivazerol decrease myocardial oxygen demand and are therefore important mechanisms for the anti-ischemic potential of alpha$_2$-adrenergic agonists.

In the present experiments, dexmedetomidine and mivazerol caused coronary vasoconstriction under normal, non-ischemic, conditions (*chapters 4, 6 and 8*). This vasoconstriction however was not associated with changes in arterial-coronary venous oxygen saturation or lactate differences, indicating adequate adaptation of myocardial blood flow to metabolic requirements (*chapter 6*).

In *chapter 4*, we showed that the systemic and coronary vasoconstriction after alpha$_2$ agonists could be alleviated by the calcium channel blocker Isradipine. If peripheral, potentially undesirable, vasoconstrictive effects of alpha$_2$ agonists would occur initially after their administration in humans, the present study indicates that the short-lasting administration of a short-acting calcium antagonist like Isradipine could be used to rapidly antagonize these vasoconstrictive effects, while having no effect on the central sympatholytic and anesthetic qualities of the alpha$_2$ agonist.

In *chapter 5*, in order to find out whether the decrease in cardiac function after dexmedetomidine was secondary to its peripheral vasoconstrictive effect, we administered the purinoceptor vasodilating agent adenosine triphosphate (ATP) to reverse the vasoconstrictive effects of dexmedetomidine. As the reversal of the vasoconstrictive effect of dexmedetomidine was associated with only partial restoration of cardiac function, we concluded that the decrease in cardiac function after dexmedetomidine is mainly due to a decrease in sympathetic outflow. This study also showed that alpha$_2$-adrenergic vasoconstriction could be completely antagonized by ATP. Extracellular ATP is converted rapidly by ecto-5'-nucleotidases into ADP, AMP and adenosine, which are important mediators of metabolic coronary vasodilation during myocardial hypoperfusion. This encouraged us to further study the interaction between alpha-adrenergic coronary vasoconstriction and metabolic coronary vasodilation.

In *chapter 6*, we investigated the effect of dexmedetomidine during reactive hyperemia after 2 minutes coronary artery occlusions. This hyperemia is known to be mainly caused by the metabolic vasodilation by adenosine. Although dexmedetomidine reduced myocardial oxygen demand and decreased blood flow in normally perfused myocardium, the supranormal blood flow levels in the endocardial and midmyocardial layers during reactive hyperemia were not influenced by dexmedetomidine. Lactate release during the reperfusion phases after dexmedetomidine were significantly less than after the alpha$_2$-antagonist atipamezole.
From our findings in chapters 5 and 6, it appeared that the vasoconstriction of alpha$_2$ agonists could be overruled by metabolic vasodilation. These findings encouraged us to further study the new alpha$_2$ agonists during experimental myocardial ischemia.

In *chapters 7 and 8*, we found that dexmedetomidine and mivazerol reduced myocardial oxygen demand and, in parallel, decreased blood flow in nonischemic myocardium. In ischemic endocardium however, blood flow was preserved. Dexmedetomidine was found to increase the ischemic/non-ischemic blood flow ratio. Both dexmedetomidine and mivazerol reduced oxygen deficiency of ischemic myocardium. The peripheral vasoconstrictive effect of dexmedetomidine and mivazerol is thus restricted to the epicardial layer during myocardial ischemia, with preservation of blood flow in the more vulnerable endocardial and midmyocardial layers. Preservation of blood flow in ischemic myocardium by alpha$_2$ agonists is probably caused by local metabolic stimuli during ischemia, which overrule adrenergic vasoconstriction. As the degree of ischemia is most severe in the inner layers during hypoperfusion, adrenergic vasoconstriction in this region is inhibited to a greater extent than in the outer layer. Specific epicardial vasoconstriction distal to a flow limiting stenosis which leads to improvement of endocardial perfusion is called the "reverse steal" effect.

The findings of these studies are now being applied to patient care. (*chapter 9*). A preliminary study on the effects of mivazerol on perioperative hemodynamic stability and myocardial ischemia was carried out in 23 centers in 300 patients and published in abstract form; the allocated patient cohort for each center was 12-13 patients. This study showed that mivazerol, when administered for 72 hours continuously perioperatively in patients at risk for coronary artery disease, decreased the incidence of tachycardia and hypertension. The incidence of bradycardia was increased in the treatment group, but there was no difference in the treatment for bradycardia. There was no increase in the incidence of hypotension in the drug group. Intraoperative myocardial ischemia was significantly lower in the alpha$_2$ agonist group, especially during the emergence period.

CONCLUSIONS

Our *experimental studies* reveal several mechanisms by which alpha$_2$ agonists may have beneficial actions during myocardial ischemia:

- the central sympatholytic effect of dexmedetomidine and mivazerol causes a reduction in heart rate and contractility, thereby reducing myocardial oxygen demand.
- during myocardial ischemia the peripheral vasoconstrictive effect of these alpha$_2$ agonists is restricted to the epicardial layer, with a preservation of blood flow in the ischemic midmyocardial and endocardial layer. The decrease in heart rate also favours endocardial relative to epicardial perfusion.

The *clinical study* showed that the administration of mivazerol is safe in high-risk patients and decreases measures of myocardial ischemia, particularly during high-stress periods.

Evidence is thus mounting that alpha$_2$-adrenoreceptor agonists may decrease perioperative myocardial ischemia. However, although postoperative ischemia is a predictor of adverse cardiac outcome,there are no definitive data demonstrating that prevention of the postoperative ischemia will reduce adverse outcome. Therefore, further study is indicated in large-scale trials assessing the effects of the alpha$_2$-adrenoreceptor agonists on cardiac outcome.

CHAPTER 11

Samenvatting en conclusies

Adrenerge receptoren bevinden zich verspreid over het gehele lichaam. Activatie van deze receptoren brengt diverse reacties teweeg. Alpha$_2$-adrenerge receptor agonisten zijn middelen die deze receptoren activeren. In 1964 werd de eerste alpha$_2$ agonist, clonidine, ontwikkeld als een ontzwellend middel van het neusslijmvlies. Patiënten die dit middel namen werden echter slaperig en kregen een lagere bloeddruk en hartslag. Daarom werd in 1966 door de farmaceutische industrie besloten om clonidine verder te ontwikkelen als een middel tegen hoge bloeddruk. De slaperigheid die dit middel teweeg brengt heeft echter het sukses van clonidine als anti-hypertensie middel sterk belemmert. De laatste jaren wordt clonidine meer en meer gebruikt in de perioperatieve periode. Clonidine blijkt immers niet alleen sederende, angstverminderende en pijnstillende effecten te hebben, maar ook kan men de dosering van anesthesiemiddelen drastisch verminderen wanneer tijdens een operatie ook clonidine wordt toegediend. Bovendien vertoont de patiënt tijdens en ook na de operatie een stabielere bloeddruk en hartfrekwentie wanneer hij clonidine heeft ontvangen tijdens de anesthesie. Recent werd in een aantal kleinere onderzoeken gesuggereerd dat, wanneer clonidine tijdens een operatie gegeven wordt aan patiënten met coronaire vernauwingen, bij deze patiënten de kans kleiner zou worden dat er myocardischemie optreedt.

In deze thesis hebben wij onderzocht of de nieuwe, specifieke en selectieve alpha$_2$-adrenerge receptor agonisten zoals dexmedetomidine en mivazerol gunstige effecten hebben wanneer zij toegediend worden in de perioperatieve periode aan patiënten met coronaire vernauwingen. Hiertoe hebben wij een aantal laboratoriumonderzoeken uitgevoerd om de potentiële anti-ischemische werkingsmechanismen van dexmedetomidine en mivazerol te onderzoeken. Speciale aandacht werd besteed aan hun sympatholytisch effect, aan hun effecten op hart en bloedvaten, en op hun effect op de doorbloeding en werking van normaal en ischemisch hartspierweefsel. Daarnaast hebben we, samen met onderzoekers van de "Multicenter Study of Perioperative Ischemia Group" van een aantal andere Europese Medische Centra, de effecten onderzocht van mivazerol op de perioperatieve stabiliteit van de hemodynamiek en op het optreden van ischemie van het hart bij 300 patiënten die een verhoogd risico hadden om aan coronaire vernauwingen te lijden.

Dexmedetomidine en mivazerol veroorzaakten beide een sympatholytische effect met een vermindering van de hoeveelheid adrenaline en noradrenaline in de bloedsomloop. De klinische dosering van 1 $\mu g \cdot kg^{-1}$ dexmedetomidine vertraagde de hartslag met 20%, deed de gemiddelde bloeddruk toenemen met 25% en verminderde het hartminutenvolume met 32% (*hoofdstukken 4,6 en 7*). Mivazerol vertraagde de hartslag met 13%, deed de gemiddelde bloeddruk toenemen met 13% en verminderde het hartminutenvolume met 43% (*hoofdstuk 8*).

In 8 honden hebben we ook linker kamer druk-volume relaties onderzocht met behulp van de conductantiekatheter, voor en na de toediening van 1 $\mu g.kg^{-1}$ dexmedetomidine. dP/dt_{max}, die een maat is voor de contractiliteit van het hart, verminderde ongeveer 10-20%, doch niet altijd significant. Deze contractiliteitsindex is afhankelijk van de preload van het hart alsook van de afterload.
De gemeten indexen van contractiliteit die niet afhankelijk zijn van pre- en afterload (end-systolic elastance en preload-recruitable stroke work), verminderden met 45% en 40%, respectievelijk. De linker kamer ejectie fractie verminderde met 35%. *(R. Frietman, J.J. Schreuder, F.W. Prinzen, P.M.H.J. Roekaerts and S. de Lange: Pressure-volume relationships in the left ventricle during use of dexmedetomidine. Ned Tijdschr Geneeskd 139 (30): 1575, 1995).*
Alpha$_2$ agonisten verminderen dus significant de contractiliteit van het hart. Het is hier echter belangrijk om op te merken dat er een zeer lange en uitgebreide klinische ervaring bestaat met clonidine en dat van dit middel nooit beschreven werd dat het nadelige gevolgen had voor het hart of voor de coronairen. Integendeel zelfs, clonidine werd met sukses gebruikt bij patiënten met coronaire vernauwingen en bij patiënten met hartfalen.
Het is de laatste jaren ook duidelijk geworden dat de correcte manier om patiënten met coronaire vernauwingen anesthesie te geven eruit bestaat om die factoren te verminderen die de zuurstofbehoefte van het hart doen toenemen. *(WK Hamilton: Do let the blood pressure drop and do use myocardial depressants! Anesthesiology 45(3): 273-274, 1976).*

De vertraging van de hartslag en de vermindering van de contractiliteit van het hart na toediening van dexmedetomidine of mivazerol veminderen de zuurstofbehoefte van het myocard en zijn daarom belangrijke mechanismen voor het anti-ischemische potentieel van alpha$_2$-adrenerge agonisten.

In de huidige experimenten veroorzaakten dexmedetomidine en mivazerol coronaire vasoconstrictie onder normale, niet-ischemische, condities. (*hoofdstukken 4,6 en 8*). Deze vasoconstrictie echter ging niet gepaard met veranderingen in de arterieel-coronair veneuze zuurstofsaturatie of melkzuur verschillen. Dit wijst erop dat er een adequate aanpassing is van de bloeddoorstroming van het hart aan de metabole behoeftes.

In *hoofdstuk 4* toonden wij aan dat de vasoconstrictie in de lichaamsbloedvaten en in de coronairen kan afgezwakt worden door de calcium-antagonist Isradipine. Indien perifere, potentieel ongewenste, vaatvernauwende effecten van alpha$_2$ agonisten zouden optreden initieel na hun toediening bij de mens, dan toont deze studie aan dat een kortdurenede toediening van het kortwerkende Isradipine snel deze vasoconstrictie zou kunnen opheffen zonder de centrale sympatholytische en anesthesie-effecten van de alpha$_2$ agonist aan te tasten.

In *hoofdstuk 5* onderzochten wij of de vermindering van de hartfunctie na dexmedetomidine secundair was aan zijn periphere effecten. Daartoe dienden wij de purinoceptor vaatverwijder adenosine triphosphate (ATP) toe om de vasoconstrictieve effecten van dexmedetomidine om te keren. Omdat het opheffen van het vasoconstrictief effect van dexmedetomidine geassocieerd was met slechts een

gedeeltelijk herstel van de hartfunctie, concludeerden wij dat de vermindering in hartfunctie na dexmedetomidine vooral te wijten is aan een verminderde sympathische outflow. Deze studie toonde ook aan dat alpha$_2$-adrenerge vasoconstrictie compleet kan geantagoneerd worden door ATP. Extracellulair ATP wordt door ecto-5'-nucleotidases snel omgezet in ADP, AMP en adenosine. Dit zijn belangrijke mediatoren van de metabole coronaire vasodilatatie die optreedt wanneer er myocardiale hypoperfusie ontstaat. Deze gegevens stimuleerden ons om verder de interactie tussen alpha-adrenerge vasoconstrictie en metabole coronaire vasodilatatie te bestuderen.

In *hoofdstuk 6* onderzochten we de effecten van dexmedetomidine tijdens reactieve hyperemie na 2 minuten durende totale coronaire afsluitingen. Deze hyperemie wordt vooral veroorzaakt door de metabole vasodilatatie door adenosine. Alhoewel dexmedetomidine zowel de myocardiale zuurstofvraag alsook de coronaire bloedstroom verminderde in normaal doorbloed myocardium, beinvloedde dexmedetomidine niet de supranormale bloedstroom hoeveelheden in de endocardiale en midmyocardiale lagen tijdens reactieve hyperemie. Het vrijkomen van melkzuur tijdens de reperfusie phasen na het geven van dexmedetomidine was significant minder dan tijdens de reperfusie phase na het geven van de alpha$_2$-antagonist atipamezole. Deze bevindingen in hoofdstukken 5 en 6 toonden aan dat de vasoconstrictieve effecten van alpha$_2$ agonisten volledig teniet gedaan kunnen worden door metabole vasodilatatie. Deze gegevens stimuleerden ons om deze nieuwe alpha$_2$-agonisten te bestuderen tijdens experimentele myocardiale ischemie.

In *hoofdstukken 7 en 8* toonden we aan dat dexmedetomidine en mivazerol de myocardiale zuurstofvraag reduceren en, in parallel, de bloedstroom in het niet-ischemische myocard verminderen. In het ischemisch endocard echter bleef de bloedstroom behouden. Dexmedetomidine bleek zelfs de ischemische/niet-ischemische bloedstroom ratio te vergroten. Zowel dexmedetomidine als mivazerol verminderden het zuurstoftekort van ischemisch myocardium. Het periphere vasoconstrictieve effect van dexmedetomidine en mivazerol blijft dus beperkt tot de epicardiale laag tijdens myocardischemie, met behoud van bloedstroom in de meer kwetsbare endocardiale en midmyocardiale lagen. Behoud van bloedstroom in ischemisch myocardium na alpha$_2$ agonisten wordt vermoedelijk veroorzaakt door locale metabole prikkels tijdens ischemie, die vasodilatatie veroorzaken die de adrenerge vasoconstrictie kan overheersen. Omdat de ernst van ischemie het ergst is in de binnenste myocard lagen tijdens hypoperfusie, zal de adrenerge vasoconstrictie in deze lagen meer geinhibeerd worden dan in de buitenste laag. Specifieke epicardiale vasoconstrictie distaal van een coronaire stenose die de bloedstroom beperkt en die leidt tot verbeterde endocardiale bloeddoorstroming noemt men het "reverse steal" effect.

In *hoofdstuk 9* hebben we, samen met de "Multicenter Study of Perioerative Ischemia Group" en de San Francisco Analyzis Group, aangetoond dat mivazerol, wanneer het 72 uur continu perioperatief werd toegediend aan 300 patiënten met een verhoogd risiko voor coronairafwijkingen, de incidentie van tachycardie en hypertensie deed afnemen. De incidentie van bradycardie was toegenomen in de mivazerol

groep, maar er was geen verschil in het aantal behandelingen voor bradycardie tussen de mivazerol groep en de placebo groep. Er was geen toename in de incidentie van hypotensie in de mivazerol groep. Intraoperatieve myocard ischemie was significant lager in the alpha$_2$ agonist groep, vooral tijdens de emergence periode.

CONCLUSIES

Onze *experimentele studies* onthullen diverse mechanismen waardoor alpha$_2$ agonisten gunstige effecten kunnen hebben tijdens myocard ischemie:
- het centrale sympatholytische effect van dexmedetomidine en mivazerol veroorzaakt een vertraging van de hartfrekwentie en een afname van de contractiliteit, met als gevolg een vermindering van de myocardiale zuurstof vraag.
- het periphere vasoconstrictieve effect van deze alpha$_2$ agonisten blijft beperkt tot de epicardiale laag tijdens myocard ischemie, met een behoud van bloedstroom in het ischemische midmyocardiale en endocardiale gebied. De vertraging van de hartfrekwentie bevoordeelt ook de endocardiale doorbloeding relatief ten opzichte van de epicardiale doorbloeding.

De *klinische studie* toont aan dat de toediening van mivazerol bij hoog-risiko patiënten veilig is en dat mivazerol de incidentie van myocardischemie vermindert, vooral tijdens de meest stressvolle periodes.

Er komen nu steeds meer aanwijzingen dat alpha$_2$-adrenerge receptor agonisten perioperatieve myocardischemie kunnen verminderen. Echter, alhoewel postoperatieve ischemie een predictor is voor 'adverse cardiac outcome', zijn er nog geen definitieve gegevens die aantonen dat het voorkomen van postoperatieve ischemie de 'adverse cardiac outcome' zal verminderen. Daarom moeten er grootschalige onderzoeksprojecten opgestart worden die de effecten van het perioperatief toedienen van alpha$_2$-adrenerge receptor agonisten op 'cardiac outcome' onderzoeken.

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Curriculum Vitae

The author of this thesis was born on March 25th, 1953 in Opglabbeek (Belgium). He attended the secondary school (Oude Humaniora) at the Sint Jan Berchmanscollege in Genk from 1965 to 1971.

He went to medical school at the Catholic University of Leuven (Belgium), where he graduaded in 1978.

He commenced his training in anesthesiology in 1978 at the University Hospital of Leiden (Head: Prof. dr. Joh. Spierdijk) and was registered as an anesthesiologist on the 1st of February 1982.

Since 1983 he has been a staff member in the Department of Anesthesiology at the University Hospital of Maastricht (Head: Prof. Dr. S. de Lange).